Case Report

OPTIC NEUROPATHY IN 2 THYROIDECTOMIZED PATIENTS WITH MODERATE TO SEVERE GRAVES OPHTHALMOPATHY FOLLOWING L-THYROXINE WITHDRAWAL PRIOR TO RADIOIODINE TREATMENT FOR THYROID CARCINOMA

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ABSTRACT

Objective: To report on 2 patients with moderate to severe Graves ophthalmopathy (GO) who developed dysthyroid optic neuropathy following levothyroxine (LT_4) withdrawal in preparation for ^{131}I treatment for thyroid carcinoma.

Methods: Two patients referred to a center for the treatment of thyroid diseases were evaluated.

Results: Patient 1, a 55-year-old woman, had active (clinical activity score [CAS], 5 out of 7] moderate to severe GO. After LT_4 withdrawal, her left eye visual acuity decreased from 10/10 to 1/10, and her omolateral visual field was impaired. Euthyroidism was rapidly restored and GO was treated with intravenous glucocorticoids. Nevertheless, as the patient's visual acuity was still impaired, orbital decompression was performed. Patient 2, a 50-year-old man, had active (CAS, 3 out of 7) moderate to severe GO. After LT_4 withdrawal, the patient developed a right dysthyroid optic neuropathy. His visual acuity decreased from 10/10 to 4/10, and his omolateral visual field was impaired. After prompt restoration of euthyroidism and treatment with intravenous glucocorticoids, normalization of his visual acuity was achieved.

Conclusion: In moderate to severe GO, dysthyroid optic neuropathy may be precipitated in thyroidectomized patients following LT_4 withdrawal, even if triiodothyronine at doses that do not prevent elevated serum thyroid-stimulating hormone concentrations are administered, suggesting that hypothyroidism should be carefully avoided in patients with such grades of GO. **(AACE Clinical Case Rep. 2015;1:e119-e122)**

Abbreviations:
CAS = clinical activity score; **DON** = dysthyroid optic neuropathy; **GD** = Graves disease; **GO** = Graves ophthalmopathy; **LE** = left eye; **LT_4** = levothyroxine; **RE** = right eye; **rhTSH** = recombinant human thyroid-stimulating hormone; **T_3** = triiodothyronine; **TRAb** = thyroid-stimulating hormone receptor autoantibody; **TSH** = thyroid-stimulating hormone; **TTA** = total thyroid ablation

INTRODUCTION

Graves ophthalmopathy (GO), an inflammatory disease likely due to an autoimmune reaction to orbital antigens, primarily affects patients with Graves hyperthyroidism. It is quite accepted that cross-reacting antigen(s) of the thyroid and the orbit induce an autoimmune response with the development of B cell– and T cell–mediated reactions that lead to the inflammatory eye manifestations (1,2). The putative antigen(s) shared by the thyroid and the orbital tissues have not been identified yet. The thyroid-stimulating hormone receptor (TSHR) is considered the most likely shared antigen, although thyroglobulin could be involved in the pathogenesis of GO as well (3).

In comparison with thyroidectomy alone, total thyroid ablation (TTA: near total thyroidectomy followed by ^{131}I ablation of the thyroid remnant tissue), which is routinely practiced for the treatment of differentiated thyroid cancer, induces a better outcome in GO treated with intravenous glucocorticoids (4-6).

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Here, we report on 2 patients with moderate to severe GO and associated differentiated thyroid cancer who developed dysthyroid optic neuropathy (DON) concomitantly to hypothyroidism due to levothyroxine (LT_4) withdrawal for thyroid remnant ablation.

CASE REPORT

Patient 1

A 51-year-old nonsmoking woman came to our observation because of Graves hyperthyroidism and GO that had developed 12 months earlier. Methimazole had been started promptly, with quick restoration of euthyroidism. Normal thyroid function had been maintained until total thyroidectomy, which we suggested because of a thyroid nodule suspicious at fine-needle aspiration. At the time of thyroidectomy, she had active GO, prevalent in the left eye (LE); her clinical activity score (CAS) was 4 out of 7, with chemosis, conjunctival redness, palpebral edema, and orbital pain. Proptosis was 23 mm in the right eye (RE) and 26 mm in the LE, with omolateral lagophthalmos. A mild impairment of the LE movements in the up-gaze was present, without diplopia. Visual acuity was 10/10 bilaterally. Blood tests showed the following: free thyroxine (FT_4), 13.1 pg/mL (normal range, 6.9 to 17 pg/mL) (Free T_4 reagent packs; Ortho-clinical Diagnostics Inc, Rochester, NY); and TSH, 0.5 μU/mL (normal range, 0.3 to 3.6 μU/mL) (Immulite 2000; Euro/DPC, Gwynedd, UK). The TSHR autoantibody (TRAb) level was 16.9 IU/L (normal range, <2 IU/L) (Brahms TRAk human RIA; Hennigsdorf, Germany).

Histology revealed a multifocal follicular variant of papillary thyroid carcinoma (primary tumor size, 2.2 cm). LT_4 (100 μg/daily) was started the day after thyroidectomy and stopped 2 weeks later to be replaced 1 week later with liothyronine (20 μg three times daily) in preparation for ^{131}I treatment. Liothyronine was discontinued within 3 weeks (2 weeks before ^{131}I treatment).

At the time of ^{131}I treatment, the patient reported symptoms of hypothyroidism and stable GO. However, at physical examination, her GO had markedly worsened, mostly in the LE; her CAS was 6/7 and her visual acuity was normal in the RE and severely reduced (1/10) in the LE. Orbital computed tomography (CT) scan demonstrated a bilateral proptosis (RE, 23 mm; LE, 26 mm), with an enlargement of the medial-rectus and inferior rectus eye muscles bilaterally and an apical compression of the optic nerves bilaterally, mainly in the left orbit (Fig. 1). Thyroid tests performed the day before ^{131}I treatment showed profound hypothyroidism, with FT_4, 1.8 pg/mL; TSH, 41.0 μU/mL; and TRAb, 14.4 IU/L.

After radioiodine treatment, euthyroidism was rapidly restored, with thyroxine (T_4; 100 μg/daily) and T_3 (40 μg/daily). GO was treated with intravenous glucocorticoid (1 g/day for 3 consecutive days and 1 g/week for 3 weeks), but the DON did not improve significantly. Therefore, the patient underwent orbital decompression (lateral in the RE; lateral plus medial in the LE), with restoration of normal visual acuity.

Patient 2

A 50-year-old nonsmoking man was admitted with the diagnosis of Graves disease (GD) with GO, which had developed 8 months earlier. He had been euthyroid since the diagnosis of GD, while taking methimazole. We advised

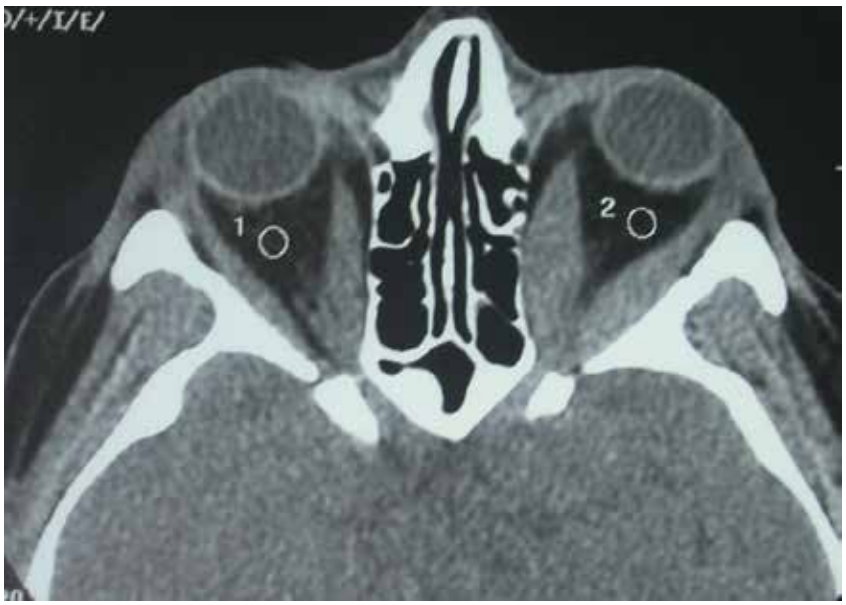

Fig. 1. Orbital computed tomography scan of patient 1, showing a severe, bilateral enlargement of extra–ocular muscles with optic nerve compression, mainly in the left orbit.

total thyroidectomy because of a large multinodular goiter (estimated volume at thyroid ultrasound, 113 mL).

At the time of thyroidectomy, ocular evaluation showed active GO, the patient's CAS was 3/7 (chemosis, conjunctival redness, palpebral edema), the proptosis was 21 mm in the RE and 23 in the LE. A mild impairment of eye movement in the up-gaze with inconstant diplopia in the peripheral gaze was present. Visual acuity was 10/10 bilaterally. At orbital CT scan, proptosis was 23 in the RE and 25 mm in the LE, and the diameter of the right and the left rectus-inferior eye muscles was 10 and 12 mm, respectively, without apical crowding. Blood tests showed the following: FT_4, 8.0 pg/mL; TSH, 2.95 μU/mL; TRAb, 2.5 IU/L.

Histology revealed a bilateral papillary thyroid cancer with tall cells in some sections. LT_4 (150 μg/day) was started the day after thyroidectomy and replaced by liothyronine (20 μg three times daily) as reported for patient 1, in preparation for ^{131}I treatment.

At the time of ^{131}I treatment, the patient reported symptoms of hypothyroidism and a severe worsening of GO a week earlier. Blood tests showed a profound hypothyroidism: FT_4, 2.9 pg/mL; free T_3, 2.2 pg/mL; TSH, 22.0 μU/mL; TRAb, 2.4 U/L. At the time of ^{131}I treatment, ocular examination showed a CAS of 4/7, with eyelid redness and swelling, conjunctival redness, and pain behind the globe. The visual acuity had worsened to 4/10 in the RE, and the patient's omolateral visual field, as well as color vision acuity, were impaired. At funduscopy, there was a swelling of the right optic disc. He was treated with ^{131}I and immediately thereafter with T_4 (150 μg/day) and T_3 (40 μg/day), with a prompt restoration of euthyroidism. Intravenous glucocorticoids were also administered (as above), resulting in a normalization of the patient's visual acuity within 3 weeks.

DISCUSSION

GO is an inflammatory disease likely due to an autoimmune reaction to orbital antigen(s) (2). Although the majority of patients with mild GO improve spontaneously with time (7), those with moderate to severe GO require active treatment (1). When treating GO, we prefer the definitive treatment of hyperthyroidism (by near total thyroidectomy or ^{131}I) because it depletes intrathyroidal autoreactive T lymphocytes and removes thyroid antigens, which are likely involved in the pathogenesis of autoimmune reactions associated with GO (1,8). The role of TTA in the disappearance of serum autoimmunity to thyroid autoantigens has been demonstrated (9,10). In addition, although this experience is not universally accepted, we showed that TTA improves the prognosis of GO (4,5).

The 2 patients we describe here underwent total thyroidectomy. Histology revealed a papillary thyroid carcinoma in both patients. We advised TTA for patient 1 because of the tumor size, the presence of tall cells in patients 2, and the multifocal pattern, age >45 years, and coexistent GD with TRAb positivity (which some authors consider a risk factor for differentiated thyroid carcinoma) in both patients (11,12). Both patients had moderate to severe GO, not requiring an urgent treatment. Unexpectedly, during the hypothyroid phase following LT_4 withdrawal for thyroid remnant ablation, GO worsened markedly up to a sight-threatening condition, which required a prompt, aggressive treatment. Our observation is novel because the onset of DON was correlated without doubt with hypothyroidism, whereas the role of treatment with ^{131}I, a possible cause of worsening GO, could be excluded.

Two putative mechanisms may be involved in the worsening of GO. The first may be related to the tissue modifications occurring during profound hypothyroidism. Overt hypothyroidism induces interstitial accumulation of glycosaminoglycans and water retention. In profound hypothyroidism, these modifications become severe, causing indurative edema of the connective tissue. As far as the orbital tissues are concerned, a "pseudo" worsening of the orbital and periorbital edema in GO patients when they are hypothyroid is commonly observed.

The second possible mechanism involves the role of hyperthyrotropinemia (elevated levels of TSH) by itself. In presence of residual thyroid tissue, the overexpression of autoantigens may boost the autoimmune reaction to the thyroid (13) and, in the setting of the postulated cross-reactivity between thyroid and orbital antigen(s), to the orbital tissue as well. These 2 mechanisms are not mutually exclusive and might coexist. It has been shown that TSH can induce the development of new fat cells in GO patients (14). A role for TRAb in adipogenesis and production of hyaluronan acid has been proposed as well (2). However, because their levels were low in one of our patients and low-medium in the other and remained unchanged after thyroidectomy, TRAb probably did not play a role in the worsening of GO we observed in these patients.

Retrospectively investigating the relationship between hypothyroidism and the course of GO in 2 groups of patients treated with ^{131}I (one receiving LT_4 only in the presence of hypothyroidism, the other immediately after ^{131}I, regardless of thyroid function), Tallstedt et al (15) showed a better outcome of GO in the latter group, concluding that hypothyroidism induced by ^{131}I treatment can exacerbate or induce the onset of GO. Similar conclusions have been recently reported by others (16).

We previously demonstrated that TTA leads to a better outcome compared with thyroidectomy alone in patients with mild to moderate GO treated with intravenous glucocorticoids (4,5). We did not observe any clinically relevant adverse effects on GO during the hypothyroid phase, subsequent to LT_4 withdrawal (4,5). At variance with our previous series, the 2 patients of the present report had a moderate to severe and active GO before thyroidectomy. A greater efficacy in treating severe to moderate GO in TTA

with recombinant human (rh)TSH administration compared with thyroidectomy alone was recently reported (6).

In order to prevent the possible worsening of GO, administration of rhTSH has been suggested as an alternative to LT_4 withdrawal for thyroid remnant ablation (17). However, Berg et al (18) described a patient with differentiated thyroid carcinoma who developed severe GO after administration of 13-cis-retinoic acid followed by rhTSH-stimulated ^{131}I therapy, and the authors pointed out that each of the 3 factors might have induced the GO. The subsequent observation of a reactivation of GO following rhTSH administration for an associated thyroid cancer suggested that high TSH levels might play a direct role in the worsening of GO (19). However, worsening of GO after thyroid remnant ablation with rhTSH in patients with moderate to severe GO treated with intravenous glucocorticoids was recently excluded (6).

CONCLUSION

In conclusion, in moderate to severe GO (in contrast to mild GO), acute hypothyroidism can precipitate DON. This phenomenon might be caused by orbital edema and requires the prompt restoration of euthyroidism and treatment of GO with anti-inflammatory drugs and eventually orbital decompression.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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