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Is Recombinant Human TSH a Trigger for Graves' Orbitopathy?

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What Is Known So Far on This Topic?

- Hypothyroidism is thought to have a detrimental effect on Graves' orbitopathy (GO), though it is unclear whether this is mediated by TSH or the hypothyroid state.
- A possible association between exacerbation of GO and use of recombinant human TSH (rhTSH) was suggested in 2005 by Berg et al. [1], who reported the development of severe GO in a patient with disseminated thyroid cancer treated with recombinant TSH, radioiodine and retinoic acid. Multiple confounding factors may have contributed to that observation.
- A recent in vitro study [2] demonstrated that the TSH receptor (TSHR) expressed in some orbital cells may be functional and respond to high TSH levels, activating intracellular signaling pathways.

What Do These Case Reports Add to Current Knowledge?

- These well-documented clinical cases of reactivation of GO after administration of rhTSH for incidental thyroid cancer support the hypothesis of the role of the TSHR in GO. Indeed the reactivation of GO appeared shortly (within 3–6 weeks) after rhTSH, while patients were euthyroid. The potential pathogenic role of exogenous high TSH reported in vitro is mirrored in vivo by our observations, thus offering a small but potentially significant contribution to resolving the enigma of the pathogenesis of GO.
- These observations should draw clinicians' attention to the risk of GO reactivation following rhTSH administration, and prophylactic steroids may need to be considered.

Key Words
Graves' orbitopathy · Thyroid cancer · Graves' disease · Radioiodine · Recombinant human TSH

Abstract
The pathogenesis of Graves' orbitopathy (GO) remains unknown. The hypothesis of a causal relationship between autoimmunity against the TSH receptor (TSHR) and GO is supported by clinical studies. Radioiodine treatment is associated with worsening or new onset of GO, possibly via antigen shedding or by inducing hypothyroidism. The coexistence of thyroid cancer with Graves' disease (GD) and GO is rare. Here we report 3 cases of reactivation of GO in patients who underwent treatment with recombinant human TSH (rhTSH) and radioiodine ablation. In each case, a thyroidectomy was performed to treat the GD, and an incidental thyroid cancer was discovered. In all 3 cases, reactivation of GO was ob-

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served 3–6 weeks after administration of rhTSH, despite maintaining euthyroidism, which was unaccompanied by a rise in serum TSHR antibodies after radioiodine and despite steroids in 1 of the 3 patients. These observations suggest that binding of either TSH or TSHR antibodies to the TSHR, independently of thyroid status, may be causally related to deterioration of GO. Clinicians should be aware of a possible association between rhTSH administration and reactivation of GO, which should be taken into account before prescribing rhTSH in patients with GO. Prophylactic steroids may need to be considered for patients at high risk of exacerbation of GO.

Introduction

Although the pathogenesis of GO remains elusive, the hypothesis of a causal relationship between autoimmunity against the TSHR and GO is supported by several in vivo and in vitro studies. Expression of the full-length TSHR is detected on orbital fibroblasts, and the demonstration of a relationship between the level of antibodies to the TSHR (TSHR-Ab) and the development of GO indicates that autoimmune reactions against the TSHR may be a prime cause of GO. TSHR-Ab are present in the serum of the majority of patients with euthyroid GO, at concentrations that correlate with the severity and activity of GO [3–5]. Radioiodine therapy is associated with worsening or new onset GO, possibly via antigen shedding and/or by inducing hypothyroidism [6–10].

Several studies have demonstrated an increased incidence of nodules and of thyroid cancer (particularly well-differentiated carcinomas) in patients with Graves' disease (GD), with reported cancer rates of 1–9% [11, 12]. The coexistence of GD with GO and thyroid cancer seems rare, with only 3 reported cases [1, 13, 14]. rhTSH is used routinely for radioiodine ablation in patients with thyroid cancer, obviating the need for hormone withdrawal and a period of hypothyroidism. In patients with thyroid cancer who happen to have GO, use of rhTSH provides an opportunity to study the effects of high serum TSH and radioiodine on the course of the orbitopathy without the potentially confounding influence of the hypothyroid state.

Patients

Case 1

This was a 52-year-old white Caucasian male smoker (15 pack-years) who had GD with unstable thyroid function for 2 years, treated with antithyroid drugs (ATD). In April 2009, he suddenly developed swelling of the right lid, right proptosis of 24 mm, painful motility restriction of the right eye leading to constant diplopia, and a clinical activity score (CAS) of 4. In June 2009, serum levels of TSHR-Ab were slightly elevated (13.6 U/l: Medizym® T.R.A.; Medipan, Berlin, Germany; upper limit of normal 12.5 U/l) and the TSH concentration was slightly above the normal limit at 3.68 mU/l (upper limit of normal 3 mU/l). In August 2009, the patient quit smoking. ATD treatment was adjusted in order to achieve euthyroidism. However, as GO remained moderately severe and active, intravenous methylprednisolone was given weekly from August to October 2009 (1 infusion/week for 6 weeks of 540 mg of methylprednisolone, followed by 6 weekly infusions of 290 mg of methylprednisolone, cumulative dose 5 g). TSHR-Ab levels became normal in September 2009 (11.8 U/l) and decreased further to 5.2 U/l in December 2009, with resolution of the inflammatory orbital parameters. Unfortunately, the patient resumed smoking in December 2009, and TSHR-Ab became positive in February 2010 (27.8 U/l). As the proptosis and diplopia persisted, a successful orbital decompression with removal of orbital fat was performed in April 2010. Due to difficulties in stabilizing thyroid function, and palpation of a nodular goiter, a total thyroidectomy was performed in November 2010. Histopathological examination revealed a 2-cm differentiated papillary thyroid cancer with initial stage pT2pN0pMx. Levothyroxine was commenced the day after surgery. As the serum TSH values measured in November and December 2010 were 4.83 and 3.76 mU/l, respectively, the dose of thyroxine was increased to 200 μg/d. The GO was inactive at this stage. In December 2010, the TSHR-Ab was 5.5 U/l (measured by Medizym T.R.A., Medipan; recalibration and restandardization with cutoff <2.5 U/l). Radioiodine ablation without steroid prophylaxis (3.7 GBq) was performed 2 days later, preceded by rhTSH (Thyrogen®, Genzyme Corporation) 0.9 mg, 48 and 24 h before radioiodine. Radioiodine treatment was administered 3 days after the first injection of rhTSH with a peak TSH on day 3 at 100 mU/l. Postradioiodine scintigraphy showed uptake in a thyroid remnant. In February 2011 (6 weeks after the radioiodine treatment), while serum TSH levels were normal (1.57 mU/l), progressive eyelid and conjunctival swelling of the left eye (CAS > 3) with proptosis and motility restriction appeared. The TSHR-Ab concentration remained elevated at 5.7 U/l (Medipan, with cutoff <2.5 U/l), but comparable to levels before the administration of rhTSH. The patient stopped smoking in April 2011, and received treatment with cyclosporin (3 mg/kg) with a moderate improvement of the inflammatory parameters. In June 2011, no thyroid remnant was detected by ultrasonography; the serum thyroglobulin (Tg) level was undetectable, but TSHR-Ab remained positive at 3.7 U/l (upper limit of normal <2.5 U/l). An orbital decompression of the left eye was performed on November 2011 with subsequent improvement of the orbitopathy.

Case 2

The second case was a 49-year-old Caucasian man, ex-smoker, treated for a multinodular goiter for 3 years with levothyroxine, which was tapered and finally interrupted because of thyrotoxic biochemistry. As hyperthyroidism persisted, carbimazole was prescribed. The hyperthyroidism persisted and proptosis with swelling of the superior lids developed, which prompted urgent referral to our department. GD was diagnosed and block-replace therapy was prescribed. The TSHR-Ab was elevated, at 59 U/l (Medipan; cutoff < 12.5 U/l), TSH was undetectable (<0.03 mU/l),

and free T3 was 7.2 pmol/l (normal range 3.3–6 pmol/l). As the multinodular goiter contained 4 nodules greater than 4 cm, and the patient had mild GO and high TSHR-Ab (59 U/l), a thyroidectomy was performed in April 2009. A 28-mm follicular variant papillary thyroid carcinoma (pT2pN0pMx) was diagnosed. Levothyroxine was commenced immediately after surgery, up to a dose of 150 μg/d. The patient was deemed suitable for radioiodine ablation, and received 3.7 GBq of radioiodine on May 15, 2009, day 3 after rhTSH stimulation at a time when the serum TSH level was measured at 51.7 mU/l. Posttreatment scintigraphy showed persistence of thyroid tissue in the thyroid bed with a measurable serum Tg (2.2 mcg/l). In June 2009, the GO became active (CAS >3), with chemosis, conjunctival injection and proptosis (26 mm in both eyes), and vertical motility restriction due to inferior rectus involvement confirmed on MRI. His serum TSH level was normal (0.28 mU/l), but TSHR-Ab remained high at 27.6 U/l (Medipan; upper limit of normal 12.5 U/l). As thyroid function was stable but GO was moderately severe and active, the patient was treated with intravenous pulse methylprednisolone weekly from August to November 2009 (cumulative dose of 7.5 g), when TSHR-Ab levels became negative. In January 2010, the reappearance of intermittent vertical diplopia coincided with a slightly elevated TSH level for 2 months (4.5 mU/l). Following adjustment of the dose of levothyroxine, the orbital inflammatory signs resolved, though the vertical diplopia persisted. The patient declined eye muscle surgery. In April 2010, no thyroid remnant was visualized on ultrasonography, Tg was undetectable, TSHR-Ab was at the lower normal level and TSH was 0.42 mU/l.

Case 3

The third patient was a 52-year-old nonsmoker Caucasian female, with type 2 diabetes. In November 2006, she noticed swelling of the right eye. Hyperthyroidism was diagnosed and treated for 3 months with antithyroid drugs. In October 2007, the hyperthyroidism and eye swelling recurred, and antithyroid drug treatment was resumed. She was found to have moderately severe unilateral GO of the right eye (proptosis 21–22 mm), with a severe vertical diplopia, due to inferior rectus restriction of the right eye. Methylprednisolone pulse therapy was commenced weekly from the end of December 2009 to February 2010 (cumulative dose 5 g). In July 2010, surgery was performed on the right inferior rectus with significant improvement of diplopia in the primary position and down-gaze. In September 2010, about 2 months after extraocular muscle surgery, edema of the eyelids and proptosis of the left eye occurred, and MRI confirmed extraocular muscle involvement due to GO. Oral prednisolone (32 mg/d) was commenced. A total thyroidectomy was performed 2 weeks later due to goiter, difficulties in stabilizing her thyroid function and presence of active GO. While continuing oral prednisolone, at tapering dosage, the orbital inflammatory signs improved significantly. Histological examination of the thyroidectomy specimen revealed a follicular variant papillary thyroid cancer (pT2pN0pMx). In November, 3.7 GBq of radioiodine was administered after 2 consecutive days on rhTSH. The serum TSH on day 3 was 185 mU/l. TSHR-Ab on November 10, 2010 was 5.8 U/l (upper limit of normal 2.5 U/l) and decreased further to 1.6 U/l in January 2011. Despite increasing the dose of oral prednisolone up to 16 mg/day, reactivation of GO with a CAS >6 occurred and proptosis increased to 24–25 mm, 20 days after the administration of rhTSH. Cyclosporin was added to the oral prednisolone with a moderate improvement of GO. In June 2011, a diagnostic radioiodine (111 MBq) scan after rhTSH administration was performed. TSH on day 3 was 146 mU/l and TSHR-Ab was 2.6 U/l. The basal and stimulated Tg remained undetectable and no uptake was visualized on the postdiagnostic scintigram. Four weeks later, the patient's eyes deteriorated again with an active (CAS >3) and moderately severe GO of the left eye. External beam radiotherapy (18 Gy) was administered. Reactivation of the GO after rhTSH was paralleled by a rise in TSHR-Ab from 2.6 U/l in June 2011 to 7.1 U/l in December 2011.

Discussion

We report 3 cases of reactivation of GO following total thyroidectomy for GD, and radioiodine treatment after rhTSH for thyroid cancer.

Radioiodine treatment may cause worsening of GO by the release of thyroid antigen resulting from radiation injury, inducing a long-lasting increase in the concentration and activity of TSHR-Ab. Smoking, high levels of pretreatment serum triiodothyronine, postradioiodine hypothyroidism and high TSHR-Ab are risk factors for the progression of GO [7].

Apart from the observation of increased TSHR-Ab after the diagnostic scan in case 3, the TSHR-Ab level was lower after radioiodine treatment than before rhTSH administration in all 3 cases, arguing against a major role of thyroid irradiation as a trigger for the aggravation of GO of our cases. These findings support the hypothesis that high levels of TSHR-Ab are not the sole cause of GO reactivation, and that other pathogenic mechanisms are probably involved.

Total thyroid ablation (radioiodine ablation after thyroidectomy) has been proposed as a means of inducing and maintaining GO inactivity, though this therapeutic strategy for GO remains controversial [15–17]. In our 3 cases, radioiodine treatment was given 3 days after the rhTSH at the peak of the TSH (>80 mU/l) without prophylactic steroid treatment. Therapeutic and diagnostic radioiodine given after rhTSH were performed under oral GC only in case 3, which did not prevent reactivation of GO. Intravenous glucocorticoid prophylaxis has been suggested as a potentially more effective means of prophylaxis against deterioration of GO after radioiodine [18].

Hypothyroidism has a detrimental effect on GO. Maintenance of euthyroidism during therapy with thioamides and prompt restoration of normal thyroid status after radioiodine therapy or thyroidectomy is highly desirable [9, 19, 20]. In our patients hypothyroidism was

prevented following radioiodine, yet reactivation of GO occurred 3–6 weeks after the administration of rhTSH and radioiodine, without a rise in serum TSHR-Ab. In our cases, GO appeared earlier after radioiodine treatment following rhTSH than the 3-month delay reported in another series where radioiodine ablation was achieved after thyroid hormone withdrawal [16]. This short latency of reactivation of GO after rhTSH is probably not coincidental, but points towards a potential role of rhTSH in the process. Compared to the study by Menconi et al. [16], the mean TSH level in our patients was twofold higher after rhTSH. The steep rise of serum TSH and the high peaks achieved after rhTSH may be instrumental in the observed rapid reactivation of GO after rhTSH.

The mechanism by which hypothyroidism leads to deterioration of GO may include overexpression of thyroid antigens driven by activation of the TSHR by high serum TSH levels. Antibodies binding to orbital TSHR may also worsen orbitopathy. rhTSH is used in patients with thyroid cancer to facilitate radioiodine ablation while keeping the patient on levothyroxine, thereby avoiding hypothyroidism [21, 22]. Following rhTSH injection, serum TSH rises severalfold above normal (often over 100 mU/l) and stays elevated for several days, while euthyroidism is maintained with levothyroxine treatment. If activation of the TSHR is instrumental in the exacerbation of GO, rhTSH administration may be expected to influence the course of GO. Thus, in predisposed patients the TSHR expressed in some orbital cells might respond to high serum TSH concentrations following rhTSH injections, through activation of intracellular signaling pathways [2].

GO is characterized by spontaneous remission and rare exacerbations. The active phase is usually self-limiting, spanning on average 18–36 months. In our cases, reactivation of GO after rhTSH occurred 18 months (cases 1 and 2) and 5 years (case 3) after the first manifestation of GO. Late reactivation of orbitopathy (after more than 5 years of quiescent disease), is an uncommon phenomenon, but occasionally occurs under euthyroid conditions with no obvious risk factors [23–25]. Franzco et al. [26] reported an incidence of 5% (8/193 patients), with a mean time interval of 12 years. The reactivation of GO of our cases could be due to the natural evolution of the disease, but its onset shortly after administration of rhTSH is unlikely to be coincidental.

Coexistence of GD with GO and thyroid cancer is rare [1, 13, 14]. In 1 of the 3 previously reported cases, GO evolved under levothyroxine suppression, but improved with intravenous glucocorticoid pulse therapy [13]. In 2 of the 3 previously reported cases, development of GO was coincident with the radioiodine treatment, but no steroid prophylaxis was prescribed. Only 1 of the 3 previously reported cases received rhTSH and reactivation of GO appeared relatively shortly (2 weeks) after radioiodine treatment without steroid prophylaxis, as in our 3 cases [1].

The exacerbation of the GO that is sometimes observed in patients with GD receiving radioiodine for control of thyrotoxicosis may be influenced by several events that follow radioiodine treatment: (1) the hypothyroid state, (2) high serum TSH, (3) the release of thyroid antigens from radiation thyroiditis and (4) a rise in TSHR-Ab (thought to be consequent upon thyroid antigen shedding). The unusual circumstances of coexistence of GO with thyroid cancer and the ability to ablate thyroid remnants after total thyroidectomy with radioiodine using exogenous TSH stimulation fortuitously allowed us to observe the effects of transient hyperthyrotropinemia on GO while the patient remained euthyroid. The exacerbation in GO that was documented in our cases suggests that the combination of high serum TSH levels, even for a few days, and radioiodine treatment were sufficient to trigger an exacerbation of GO. The relative importance of these two factors (high TSH and radioiodine treatment) in inducing exacerbation of GO is unclear.

Our observations are consistent with the hypothesis that activation of the TSHR in extrathyroidal tissues, whether by TSH or by TSHR-Ab is key to the pathogenesis of GO, and that the hypothyroid state may be of lesser importance. Clinicians treating patients with rhTSH ought to be aware that rhTSH can trigger reactivation of GO. Prophylactic steroid treatment should be considered in patients at risk of progression of GO who are scheduled to receive rhTSH.

Further studies and careful follow-up of such cases may aid in defining the pathogenesis of GO and evaluate the incidence of such recurrence.

Disclosure Statement

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