Clinical case

Graves’ ophthalmopathy after total thyroidectomy for papillary carcinoma

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Available online 31 December 2010

Résumé


Mots clés : Orbitopathie basedowienne ; Maladie de Basedow ; Carcinome papillaire

Abstract

We report the case of a 53-year-old woman who underwent two-phase total thyroidectomy (June and December 2001) for a multinodular goiter with incidental discovery at the first procedure of a multicentric papillary carcinoma of the right thyroid lobe. Thyroidectomy was followed by an ablative dose of 131-radioiodine because of the presence of residual tissue in the neck. The various elements of the follow-up are reassuring: no residual tissue was detected at the ultrasonography of the neck and thyroglobulin was undetectable in the absence of antithyroglobulin autoantibodies. In April 2006, the patient developed unilateral Graves’ ophthalmopathy with the appearance of antithyrotropin receptor autoantibodies (TRAb). Ophthalmopathy progressively improved, in parallel to the decrease of TRAb. The parallel trend of TRAb and the ophthalmopathy supports the major role of TRAb in the pathogenesis of thyroid-associated ophthalmopathy. This observation also shows the possibility of developing autoantibodies in the absence of detectable thyroid tissue.

Keywords: Graves’ ophthalmopathy; Graves’ disease; Papillary carcinoma

The pathophysiological mechanisms of Graves’ ophthalmopathy remain unclear. The main element is the TSH receptor, which remains the most likely candidate as an autoantigen. TSH receptors should be present on the surface of the orbital fibroblasts like in the thyroid cells. A number of studies have demonstrated a significant correlation between the level of TRAb, and the occurrence and severity of Graves’ ophthalmopathy (GO) [1].

We report the case of a patient who developed GO after total thyroidectomy for papillary thyroid cancer.

1. Case report

A non-smoking 53-year-old woman with no family history of thyroid disease or personal history of Graves’ disease attended our unit in December 2000 for examination of a voluminous thyroid nodule, which had been discovered fortuitously in the right lobe.

She was free of any signs of hyperthyroidism or GO; the thyroid profile was as follows: TSH = 1.2 µU/mL...
(normal range, 0.25–5); T4 = 18 pmol/L (normal range, 10–25), T3 = 4.7 pmol/L (normal range, 3.1–6.1). Blood calcitonin level was in the normal range, and antithyroid peroxidase (TPOAb), antithyroglobulin (TgAb) and TSHR autoantibodies (TRAb) were negative. The ultrasonography confirmed the presence of a heterogeneous necrotic right lobe nodule measuring 34 × 25 mm with many microcysts. A fine-needle aspiration biopsy was non-contributory.

Right lobo-isthmectomy was performed in June 2001: the nodule was benign on the frozen-section analysis, as well as in the final histological examination.

The final histological assessment resulted in the discovery, distant from this nodule, of a right infiltrating papillary carcinoma measuring 0.2 cm, with seven or eight other zones of inframillimetric carcinoma. One of these was located in contact with conjunctive tissue of the thyroid capsule without infiltrating it. The histology of the left lobe was totally negative, with no localization of papillary carcinoma. Total thyroidectomy was performed in December 2001, without systematic lymph node dissection.

In March 2002, an ultrasonography showed the presence of a richly vascularized right laterotracheal formation measuring 15 mm, with an aspect suggestive of residual thyroid tissue. Because of this image, in June 2002 the patient subsequently received, after levothyroxine withdrawal, an ablative dose of 131-radioiodine (131; 100 mCi).

The post-therapy whole body scan showed a reduction in size of the residual tissue, measuring 7 mm on ultrasonography with no other uptake.

In March 2003, a new whole body scan (131, 5 mCi) after levothyroxine withdrawal, did not show any iodine-accumulating tissue.

Levothyroxine suppressive therapy at 100 µg was continued, the patient was re-evaluated every 6 months, then annually: TSH levels were between 0.20 and 0.4 µU/mL (normal range, 0.25–5 µU/mL); T4 and T3 remained in the normal range, thyroglobulin was undetectable; TgAb were negative.

An ultrasonography did not show any residual thyroid tissue, nor pathological adenopathy (two non-vascularized, non-specific left jugular micronodules). Neck palpation was normal.

In April 2006, the patient consulted for left retrobulbar pain, exophthalmia which had developed over 6 months without visual deterioration or diplopia. She was treated with levothyroxine 100 µg/day.

Ophthalmological examination confirmed the suspected unilateral GO: grade II exophthalmia, upper lid retraction, lid lag, without any abnormality of the oculomotoricity, or any major clinical signs of inflammation.

The orbital magnetic resonance imaging (MRI) confirmed the grade II exophthalmia, with an enlargement of the muscles and the orbital fat compatible with GO (Fig. 1).

MRI did not show the presence of other lesions in the orbit or in the brain. Measurement of thyroid hormones revealed a suppression of TSH <0.05 µU/mL, an increase of T4 at 2.68 ng/dL (NR: 0.8–1.9 ng/dL) and a normal level of T3. TPOAb and TgAb were undetectable whereas TRAb was now detectable at 8 IU/L (NR < 1 IU/L).

Thyroglobulin was undetectable. Ultrasonography as well as thoraco-abdominal computed tomography were negative.

Levothyroxine was decreased (alternation 100 and 75 mcg), the ophthalmopathy was treated by local care. The patient was followed with serial determination of thyroid hormones, thyroid autoantibodies, physical and ophthalmological examination. TRAb levels decreased gradually, returned to the normal range in June 2008 until the last consultation in November 2009. In parallel, the ophthalmopathy improved significantly. In November 2009, the patient had moderate non-progressive exophthalmia.

2. Discussion

The appearance of TRAb after 131-radioiodine treatment is a known phenomenon.

Some studies have reported the occurrence of hyperthyroidism in parallel with positivity of TRAb in previously TRAb-negative patients treated by 131 for a toxic nodular goiter [2,3]. In most cases, TRAb appeared 3 to 12 months after 131 therapy and spontaneously disappeared over 12 months.

Several studies have found increased TgAb or TPOAb levels in patients with thyroid cancer after total thyroidectomy and 131 therapy [4–6].

A case of bilateral exophthalmos with TRAb occurring 9 years after total thyroidectomy for a papillary thyroid carcinoma was reported in the presence of metastasis [7]. However in this patient Ab had not been measured before surgery and 131 therapy.

Fig. 1. Orbital MRI, normal aspect of the right orbit. Left orbit: grade II exophthalmia. Enlargement of the extraocular muscles and orbital fat. Absence of another intra-orbital lesion.

Another case of GO with TRAb was reported 40 years after a total thyroidectomy for a papillary carcinoma, in the presence of vertebral metastasis [8].

Antonelli et al. reported a case similar to ours, of GO and TRAb which occurred 4 years after total thyroidectomy and 131I therapy for papillary thyroid carcinoma [9]. In our patient antibodies (TPOaB, TgAb, TRAb) were negative before the thyroidectomy and 131I therapy; TRAb activity and exophthalmia appeared simultaneously approximately 5 years later, in the absence of recurrence or metastasis of cancer.

Subsequently TRAb progressively decreased, in parallel with the improvement of ophthalmopathy, and disappeared 6 years after the thyroidectomy and 131I therapy. This delay is similar to that reported in a study showing the disappearance of TRAb in 182 patients, who were treated with thyroidectomy and 131I for papillary carcinoma and followed for 10 years [10].

Our observation supports previous reports of increases in TRAb levels after 131I therapy for nodular goiter, which in most cases spontaneously disappear.

In contrast with published cases of GO in patients with cancer, except for the case reported by Antonelli et al., no detectable metastases were present in our patient, proving that the presence of thyroid tissue (normal or pathological) is not necessary for the development of thyroid autoantibodies.

It is nevertheless important to underline that TRAb developed several years after 131I therapy, so it is not possible to formally confirm the role of this therapy in the induction of the thyroid autoimmunity. We cannot absolutely exclude the fortuitous character of the thyroid autoimmunity and the occurrence of an isolated form of GO (euthyroid Graves’ disease), nor the persistence of residual microcarcinoma, potentially functional, at the origin of an increase of Graves’ disease.

Furthermore, the presence of TRAb had no impact on the evolution of thyroid carcinoma, which remained in complete remission according to various clinical, biological and radiological criteria.

Indeed, a number of studies have suggested an increased aggressiveness of papillary thyroid carcinoma (multifocality, occurrence of distant and locoregional lymph node metastasis) in Graves’ disease patients, despite the suppression of TSH under treatment. TRAb apparently plays an important stimulating role in this poor outcome of carcinoma [11–14]. Nevertheless, this effect is still discussed and with some authors totally disagreeing [15].

In our patient treated with thyroidectomy and 131I therapy for a non-metastatic and multicentric papillary thyroid carcinoma, TRAb with unilateral GO appeared 5 years later. The parallel time course of TRAb and GO reinforces the hypothesis that TRAb plays a causal role in the pathogenesis of GO, supported by several studies [1,16].

It is of interest to note that the patient developed TRAb (initially absent) when she had no detectable thyroid tissue as demonstrated by the search for serum thyroglobulin (negative from 2006 to 2009) and various scans. This would appear to suggest that the antigen can arise from a tiny fragment of undetectable thyroid tissue, or even come from orbital tissue (orbital fibroblasts?).

Conflict of interest statement

The authors do not have any conflict of interest.

References