Pathological Findings of the Thyroid Tissue in a Patient with Euthyroid Graves' Disease

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Abstract

Euthyroid Graves' disease (EGD) is a rare condition marked by the onset of thyroid-associated ophthalmopathy (TAO) in the absence of thyroid dysfunction. The pathogenesis of EGD remains unclear, and a consistent view of the pathological findings of the thyroid tissue has yet to be determined. We herein report a case of EGD in a 34-year-old woman with papillary carcinoma treated with total thyroidectomy. The entire thyroid specimen was investigated, and the thyroid tissue appeared normal. In this report, we discuss the relationship between the pathogenesis of TAO and thyroid dysfunction.

Key words: Euthyroid Graves' disease, thyroid-associated ophthalmopathy, pathological changes in thyroid tissue

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Introduction

Thyroid-associated ophthalmopathy (TAO) is characterized by immune-mediated inflammation of the extraocular muscles surrounding the orbital connective and adipose tissue and generally occurs in patients with hyperthyroidism due to Graves' disease. Euthyroid Graves' disease (EGD) is a condition marked by the appearance of TAO against a background of a normal thyroid function. Among the types of TAOs, EGD reportedly shows a prevalence of 0.7-21% (1). Although EGD was first reported by Rundle and Wilson in 1945 (2), the pathogenesis continues to remain unclear; some authors have suggested that this pathology represents a prodromal stage of Hashimoto's thyroiditis or Graves' disease (3). Excluding results obtained from needle biopsies, a consistent view of the pathological findings of the thyroid tissue has yet to be determined, and case reports are lacking. We herein report a case of EGD with papillary carcinoma in which total thyroidectomy was performed.

Case Report

A 34-year-old Japanese woman presented to an ophthalmologist with a 5-month history of dry eyes and photophobia and a 3-month history of swelling of the right eyelid. After undergoing examinations, she was referred to our clinic for an evaluation of the thyroid function. She was euthyroid without treatment with any medications. The serum levels were as follows: free triiodothyronine, 2.8 pg/mL (reference range, 2.2-4.3 pg/mL); free thyroxine, 1.44 ng/dL (reference range, 0.80-1.60 ng/dL); and thyrotropin, 0.97 µU/mL (reference range, 0.20-4.50 µU/mL). The titer of thyrotropin receptor antibodies (TRAb) was 2.6 IU/L, [third-generation competitive receptor assay using thyroid stimulating hormone (TSH) receptor monoclonal antibody, electrochemiluminescence immunoassay; reference range, <2.0 IU/L] and the titer of thyroid-stimulating antibodies (TSAb) was 236% [Bioassay+Radio-immunoassay, (4); reference range, <180%], whereas negative results were obtained for thyroid-stimulating blocking antibodies (TSBAbs) 34%; [Bioassay+Radio-immunoassay, (5); reference range, <40%], anti-thyroglobulin antibodies (TgAb) 11.1 IU/mL; (enzyme-

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Figure 1. Magnetic resonance imaging of the orbit shows enlargement of the rectus and upper eyelid muscles.

Figure 2. Thyroid imaging with ultrasonography. The thyroid appears isoechoic on ultrasound, which does not suggest the presence of Hashimoto's thyroiditis. 1) Longitudinal image: the tumor appears as a low-echoic lesion. 2) Axial image: the entire thyroid.

immunoassay; reference range, ≤ 40 IU/mL) and anti-thyroid peroxidase antibodies (TPOAb) 12.5 IU/mL (enzyme-immunoassay; reference range ≤ 28 IU/mL). The thyroid was not palpable, and the estimated thyroid volume measured on ultrasonography was 12 mL. Exophthalmos and retraction of the right eyelid were observed; the exophthalmometry measurements were 19 mm for the right eye and 17 mm for the left eye, with an eyelid fissure of 9 mm on the right and 8 mm on the left. Magnetic resonance imaging demonstrated hypertrophy of the right inferior rectus and upper eyelid muscles; however no tumors or inflammation were noted (Fig. 1). EGD was diagnosed based on these findings, and the Clinical Activity Score (CAS), which is used to evaluate the activity of TAO, was 1. The local injection of triamcinolone into the right eyelid was performed to treat the ophthalmopathy. In addition, thyroid ultrasonography showed a 5-mm low-echoic nodule in the left lobe (Fig. 2), and an aspiration biopsy revealed papillary carcinoma. The positive TRAb and TSAb titers suggested a risk of hyperthyroidism in the near future. The patient was hoping to become pregnant and was worried about the potential side effects of anti-thyroid drugs that may be required during pregnancy. Considering these circumstances, total thyroidectomy was performed eight months after the diagnosis of EGD. During this period, the thyroid function remained within the normal limits, despite the positive TRAb and TSAb. A whole thyroid specimen was investigated; however, no findings typical of Hashimoto's thyroiditis, lymphocytic infiltration, fibrosis, Graves' disease or cellular hypertrophy or hyperplasia were seen, and the thyroid tissues appeared to be normal (Fig. 3).

Figure 3. Hematoxylin and Eosin staining of the thyroid tissues showing neither hypertrophy nor hyperplasia. 100× magnification. No findings suggestive of Hashimoto's thyroiditis were identified.

Postoperatively, the patient has remained under treatment with oral thyroid hormone replacement therapy consisting of levothyroxine at a dose of 100 µg/day. The TRAb titer became negative 7 months after thyroidectomy (1.1 IU/L).

Discussion

TAO is primarily related to hyperthyroidism, although it sometimes occurs with other types of thyroid disorders. Bartley et al. (6) reported that 90% of TAO patients have hyperthyroidism, 0.8% have hypothyroidism, 3.3% have Hashimoto's thyroiditis and 5.8% are euthyroid. The most common presenting symptoms of TAO are ocular surface discomfort, periorbital swelling, retro-orbital pain, gaze-provoked pain and diplopia (7). TAO is usually bilateral, with only 10-15% of patients showing asymmetrical symptoms (8).

Environmental factors, such as infection or smoking, have been suggested to influence the onset of TAO (9). A previous report showed that a male gender and advanced age at the time of diagnosis of TAO are related to severe ophthalmopathy (10). Our patient was a young woman who reported no history of severe infection or smoking.

Some hypotheses suggest that factors such as TRAb, insulin-like growth factor-1 receptor, cytokines and extraocular muscle antigens are involved in the development of TAO (11). Among these factors, only the TRAb titer was investigated in the present case.

There is also no consistent view as to the pathological findings of the thyroid tissue in patients with TAO. Some authors have suggested that this pathology represents a prodromal stage of Hashimoto's thyroiditis or Graves' disease (3), whereas others have reported that the histology of the thyroid tissue obtained via needle biopsy shows inflammatory and/or, degenerative changes or simple epithelial hyperplasia (12-14). Tamai et al. (3) reported the pathological findings of the thyroid tissue obtained via needle biopsy, with seven of nine cases exhibiting Hashimoto's thyroiditis,

and the remaining displaying diffuse hyperplasia. Similarly, Kosugi et al. reported that two of their nine cases showed slight inflammatory or degenerative changes, while the remaining seemed to have normal thyroid tissue (14). Furthermore, Kasagi et al. (13) reported the histology in four cases. In that report, two patients positive for TSAb showed epithelial hyperplasia, while the other two patients demonstrated minimal degenerative changes. In addition, one of the latter patients was positive for anti-TgAb, anti-TPOAb, TBII and TSAb, whereas the other patient was positive only for TSAb. The discrepancies between the results of Tamai et al. and the findings observed in our case may be due to the fact that patients with Hashimoto's thyroiditis have tended to be collected in such reports; most previous cases have been positive for anti-thyroid antibodies. That is to say, the presence of a large goiter has a major effect on the decision to perform a biopsy.

In cases of Graves' disease, the thyroid tissue exhibits cellular hypertrophy and hyperplasia on microscopic examinations. In contrast, microscopic examinations in patients with Hashimoto's thyroiditis show many small follicles, a decreased amount of colloid particles and the extensive infiltration of lymphocytes, plasma cells and macrophages. In the current patient, no typical findings of Hashimoto's thyroiditis or Graves' disease were evident in a whole thyroid specimen. Several hypotheses as to why EGD patients may remain in a euthyroid state have been put forward, including a small thyroid (12, 15), destruction of the thyroid due to Hashimoto's thyroiditis (3, 12, 14, 16, 17) or the weaker effect of TSAb derived from EGD patients in stimulating cAMP production than that required for the synthesis or release of thyroid hormones compared to the hyperthyroidism observed in patients with Graves' disease (12, 14-17). However, which of these mechanisms are applicable remains uncertain. We have encountered patients with hyperthyroid Graves' disease in whom the thyroid was almost normal in size and reported in the present case that the thyroid tissue from a patient with EGD appeared to be completely normal. Considering these observations, although there may be a correlation between the thyroid function and the size of the thyroid, abnormal reactivity of the thyroid and/or the signaling system involving cAMP, the first two hypotheses appear unlikely in this case. On the other hand, the last hypothesis remains a possibility, although the cAMP titer is measured on radio-immunoassays *in vitro*, and we have no evidence regarding how TSAb may differently stimulate cAMP production *in vivo*. Sato et al. reported a significant correlation between the TSAb titer and the thyroid hormone-releasing activity in an experiment using porcine thyrocytes (18); however, the results were obtained *in vitro*. In addition, as we were unable to examine the cAMP titer in the thyroid follicular cells from the current patient *in vivo*, it was not possible to clarify the relationship between ophthalmopathy and the thyroid function in this case. Further analyses are expected.

The authors state that they have no Conflict of Interest (COI).

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