Graves' disease with an autonomously functioning thyroid nodule

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autonomous thyroid
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ABSTRACT

We present the case of a 68-year-old woman with Graves' disease, orbitopathy and an autonomously functioning thyroid nodule. Initially, the patient was diagnosed with orbitopathy as a sign of euthyroid Graves-Basedow's disease, confirmed by the presence of thyrotropin receptor antibodies. Five years later symptoms of hyperthyroidism occurred. Thyroid scan with iodine-131 (^{131}I) showed a hot nodule in the right lobe. Recurrences of hyperthyroidism and short remissions were observed in the course of the disease – the symptoms typical of hyperthyroidism due to an autonomously functioning thyroid nodule. Fine needle aspiration biopsy of the nodule revealed no atypical follicular cells and the patient was scheduled for ^{131}I treatment. She has been euthyroid for over one year.

INTRODUCTION Diagnostic procedures for thyroid disorder include biochemical evaluation: measurement of serum thyrotropin (TSH), free thyroid hormone (free thyroxine [FT_4], free triiodothyronine [FT_3]) and thyroid antibody levels, as well as imaging including ultrasonography (USG) and thyroid scan. In some cases fine needle aspiration biopsy (FNAB) should be performed. These procedures usually allow to reach a definite diagnosis.

TSH secretion is regulated primarily by thyroid hormone negative feedback, especially by FT_3 . Its low levels enhance and high levels suppress TSH secretion, as occurs in hypothyroidism and hyperthyroidism, respectively.

Apart from hormone tests, the antithyroid antibody assay is also important in the diagnosis of thyroid disorders. Human thyrotropin receptor antibodies (TRAb) are known causative factors of hyperthyroidism in Graves' disease. Thyrotropin receptor antibody assay is useful in differential diagnosis, particularly in uncertain cases. There are two types of antibodies directed against TSH receptor, i.e. thyroid stimulating immunoglobulins (TSI), which stimulate thyroid cell and hormone production, and thyroid blocking antibodies (TBAb). Hyperthyroidism is associated with high TSI levels. In patients with both types

of antibodies, the thyroid disorder is characterized by high variability, with periods of hypothyroidism, hyperthyroidism and euthyroid state.¹

USG, which is the primary procedure for evaluating the volume and structure of the thyroid gland, enables to identify thyroid nodules and suspect autoimmune process. Increased blood flow in power Doppler ultrasound confirms Graves' disease as the cause of hyperthyroidism.

Radioisotope imaging of the thyroid gland (thyroid scan) is performed mainly in patients with thyroid cancer, to evaluate iodine-131 (^{131}I) uptake or to detect an autonomously functioning thyroid nodule prior to ^{131}I treatment of hyperthyroidism.¹

Graves' disease is the most common cause of primary hyperthyroidism (50–80% of hyperthyroid patients). The incidence of Graves' disease depends on iodine uptake in the study population. Typical symptoms, associated with autoimmune mechanisms, include exophthalmos, thyroid bruit and pretibial myxedema. Thyroid scan of Graves' patients shows an equal radioisotope uptake in both lobes. Patients with new-onset disease receive pharmacological treatment. In the case of side effects or recurrence of hyperthyroidism, radioactive iodine or subtotal thyroidectomy are performed.^{1,2}

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	1999	2007 (before radioiodine therapy)	2008 (after radioiodine therapy)
TSH	0.06 (μIU/ml)	0.01 (μIU/ml)	0.49 (μIU/ml)
FT ₄	42.0 (pmol/l)	21.4 (pmol/l)	15.3 (pmol/l)
FT ₃	12.0 (pmol/l)	5.1 (pmol/l)	
anti-TPO	>600 (IU/ml)	>600 (IU/ml)	>600 (IU/ml)
hTRAb	15.4 (IU/l)	0.3 (IU/l)	0.5 (IU/l)
thyroid scan ¹³¹ I

FIGURE Imaging of the thyroid gland and laboratory investigations during follow-up; normal ranges – TSH 0.3–4.3 μIU/ml, FT₄ 11.0–22.0 pmol/l, FT₃ 3.1–6.8 pmol/l, anti-TPO 0.0–50.0 IU/ml, hTRAb 0.0–1.0 IU/l. Abbreviations: FT₃ – free triiodothyronine, FT₄ – free thyroxine, hTRAb – human thyrotropin receptor antibodies, TPO – thyroid peroxidase, TSH – thyrotropin, USG – ultrasonography, ¹³¹I – iodine-131

Solitary toxic nodule (Goetsch's disease) occurs in approximately 30–40% of hyperthyroid patients with nodular goiter. In about 60% of these cases, multinodular autonomic goiter (Plummer's disease) is observed. A hot nodule in the thyroid scan is observed in patients with Goetsch's disease. In treating hyperthyroidism caused by toxic nodular goiter, ¹³¹I or thyroidectomy are preferred over pharmacological treatment which should only be used on a temporary basis.¹

We present a rare case of Graves' disease coexisting with an autonomously functioning thyroid nodule, a condition known as the Marine-Lenhart syndrome.

CASE REPORT The patient, born in 1940, has been under the care of endocrinology clinic for over 20 years. Initially, she was treated with thyroid extract for simple goiter. In 1988, thyroid orbitopathy without symptoms of hyperthyroidism occurred (the diagnosis of euthyroid Graves' disease was based on clinical symptoms as thyrotropin receptor antibody assay was not available at the time). The patient had been treated with titrated doses of synthetic glucocorticosteroids (dexamethasone) for approximately 6 months. Her eye condition improved. First symptoms of hyperthyroidism occurred in 1993. Antithyroid drug therapy (ADT), followed by ADT and L-thyroxine (block and replace method) were successfully used. Hyperthyroidism recurred in 1995, when the patient stopped the medications and routine thyroid screening. In the following years, recurrence of hyperthyroidism was observed each time ADT was reduced. It was not possible to

schedule radical treatment due to a lack of regular checkups. Thyroid USG disclosed a solitary nodule of 25 × 30 mm in the right lobe. FNAB yielded blood and protein content, monomorphic follicular cells with macronucleosis and nuclear polymorphism. Toxic diffuse goiter was suspected. In 1997, anti-thyroid peroxidase (TPO) antibodies were assayed (>600 IU/ml, normal range: 0–50 IU/ml). In 1999, anti-TSH receptor antibodies were measured (15 IU/l, normal range: 0–1 IU/l, radioimmunoassay, TRAK human, B.R.A.H.M.S.). In 1995, thyroid scan was performed for the first time, showing a prominent radioiodine uptake mainly in the right lobe, which is not typical in patients with Graves' disease. In 2007, a repeated scan showed a hot nodule in the right lobe and no ¹³¹I uptake in the left lobe. Multinodular right lobe with a dominant nodule (27 × 15 mm) was found on USG. Protein, blood cells, macrophages, and normal follicular cells were detected on FNAB and the patient was scheduled for ¹³¹I treatment. Laboratory tests showed normal serum levels of TRAb and high serum levels of anti-TPO. ADT was stopped 10 days before ¹³¹I administration. Six weeks after ¹³¹I therapy, normal levels of FT₃ and FT₄, low serum levels of TSH, and clinical euthyroidism were observed. A year after the therapy, the patient remained clinically and biochemically euthyroid. Thyroid scan showed heterogeneous ¹³¹I uptake with a dominance of the right lobe and a low uptake in the left lobe, which corroborated high efficacy of the treatment and damage to the thyroid tissue within an autonomous nodule (FIGURE).

DISCUSSION Thyroid nodules are present in 13–20% of all patients with Graves' disease³; however, coexistence of Graves' orbitopathy and toxic nodular goiter is rare (0.05–0.2% of patients with Graves' disease)⁴. Only 3 such cases have been recorded over the last 10 years at the Department of Endocrinology in Köln, Germany.⁴

Our patient presented with orbitopathy as the first symptom in the course of Graves' disease, confirmed by the presence of anti-TSH receptor antibodies in serum. Thyroid function depends on the type of antibodies (stimulating or blocking) present in patients. Orbitopathy without concomitant hyperthyroidism is known as euthyroid Graves' disease. In our case, hyperthyroidism developed 5 years after the onset of orbitopathy. Its pathogenesis might have been as follows:

- 1 Initially, hyperthyroidism was caused by Graves' disease (high TRAb titer, FNAB results suggesting diffuse goiter) and later developed due to an autonomously functioning thyroid nodule.
- 2 Both mechanisms operated throughout the course of the disease (as observed on thyroid scan).
- 3 Hyperthyroidism was induced by an autonomously functioning thyroid nodule alone in the right lobe, while orbitopathy was the only manifestation of euthyroid Graves' disease.

Our patient experienced several relapses with short periods of remission, which is typical in hyperthyroidism caused by toxic nodular goiter. Hyperthyroidism at the later stage of the disease, with simultaneous low TRAb titer, also suggests that the condition was caused by an autonomously functioning thyroid nodule. Thyroid scan indicates that the autonomously functioning thyroid nodule rather than Graves' disease was an etiological factor, or that the two mechanisms coexisted. Moreover, hyperthyroidism did not develop in the first 5 years (1988–1993) of euthyroid Graves' disease presenting with orbitopathy.

A similar course of thyroid disorder was observed by Michigishi et al. in a 39-year-old male patient with Graves' ophthalmopathy, who underwent surgery due to unequivocal FNAB results. He was finally diagnosed with papillary thyroid carcinoma. Hyperthyroidism was associated with an autonomously functioning thyroid nodule, and the only manifestation of Graves' disease was orbitopathy.⁵ We believe that the etiology of hyperthyroidism in our patient was equally complex.

Recently, an increased risk of malignant thyroid nodules in patients with Graves' disease has been brought to attention. The risk may be associated with the presence of stimulating antibodies, which cause cell proliferation.^{6,7} Therefore, it becomes necessary to optimize therapeutic approach in these patients. The choice of treatment should not be made without considering additional laboratory tests, as well as all indications and contraindications to the available options of radical treatment.

We decided on ¹³¹I therapy for the following reasons:

- 1 In toxic nodular goiter thyroid cancer is rare. There have only been a few cases reported.^{5,7,8}
- 2 FNAB tests performed twice showed no atypical follicular cells.
- 3 Surgery was excluded for cardiovascular reasons.

Frequent relapses and difficulty in achieving euthyroidism resulted from an atypical course of Graves' disease, probably concomitant with an autonomously functioning thyroid nodule – the primary cause of her hyperthyroidism – from the beginning.

The ¹³¹I treatment proved effective and we consider it the best therapeutic modality.

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Współwystępowanie autonomicznego guzka tarczycy z chorobą Gravesa-Basedowa

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SŁOWA KLUCZOWE

autonomiczny guzek tarczycy, leczenie radiojodem, nadczynność tarczycy, orbitopatia

STRESZCZENIE

Opisano przypadek 68-letniej pacjentki z chorobą Gravesa-Basedowa przebiegającą z objawami orbitopatii i współistniejącym gorącym guzkiem tarczycy. W początkowym okresie obserwacji rozpoznano orbitopatię jako objaw choroby Gravesa-Basedowa, potwierdzonej obecnością przeciwciał przeciwko receptorowi dla tyotropiny, przebiegającej z eutyreozą. Po pięciu latach od rozpoznania orbitopatii tarczycowej u chorej wystąpiły objawy nadczynności tarczycy, z obecnym w badaniu scyntygraficznym gorącym guzkiem prawego płata. W dalszym przebiegu choroby obserwowano częste nawroty nadczynności tarczycy z bardzo krótkimi okresami remisji, co jest typowe dla nadczynności tarczycy powodowanej przez guzek autonomiczny tarczycy. Biopsja cienkoigłowa guzka nie wykazała obecności atypowych komórek pęcherzykowych i chorą zakwalifikowano do leczenia radiojodem. Rok po terapii chora nadal pozostaje w eutyreozie.

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