NOTE

Coexistence of an Autonomously Functioning Thyroid Nodule in a Patient with Graves' Disease: An Unusual Presentation of Marine-Lenhart Syndrome

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Abstract. A 44 year-old woman developed hyperthyroidism due to the coexistence of Graves' disease and an autonomously functioning thyroid nodule (AFTN). Anti-thyrotropin receptor antibody (TRAb) was strongly positive (83.2%), and a thyroid scan initially showed diffuse uptake of Tc-99m pertechnetate in both lobes and further increased uptake in accordance with the right lobe nodule. The nodule in the right lobe was histologically diagnosed as thyroid follicular adenoma. After she was maintained in a euthyroid state by treatment with Methymazole (MMI), thyroid uptake of Tc-99m in the nodule became lower and was slightly suppressed by T3 administrations probably due to its dependence on TSH. Subtotal thyroidectomy was performed and she subsequently became euthyroid with negative TBI activity. It is concluded that she had a coexisting functioning nodule with Graves' disease (Marine-Lenhart syndrome) and that the nodule changed from hot to cool along with the anti-thyroid treatment, unlike usual cases of this syndrome showing a cold nodule on the initial imaging under the hyperthyroid state. Repeated Tc-99m pertechnetate thyroid scans were helpful in evaluating the reaction of MMI and TSH in both lesions separately in the present case.

Key words: Graves' disease, Autonomously functioning thyroid nodule (AFTN), Thyrotoxicosis, Marine-Lenhart syndrome, Scintigraphy

HYPERTHYROIDISM is the condition resulting from the effect of excessive circulating thyroid hormones. The common causes of hyperthyroidism are Graves' disease and autonomously functioning thyroid nodules (AFTN). These two diseases are quite separate clinical entities. The pathophysiology of Graves' disease is distinctly different from that of AFTN; whereas the former is caused by the activation of thyrotropin receptor by anti-thyrotropin receptor antibody (TRAb), the latter is caused by hyperfunctioning nodules and extranodular tissues are regulated under a normal pituitary-thyroid feedback system. We report a patient with Graves' disease who simultaneously had a thyroid follicular adenoma with higher Tc-99m pertechnetate thyroid uptake than the extranodular thyroid tissue.

Case Report

A 44-year-old woman was transferred to Kansai Medical University Hospital in July, 1994 from another hospital because of laboratory test results compatible with hyperthyroidism. She presented with a one month history of fine finger tremor and palpitation. She denied any family history of...
thyroid or autoimmune disease.

On physical examination, a diffusely enlarged thyroid gland with a solitary nodule (3.6 x 2.8 cm) in the right thyroid lobe was palpated. She had no evidence of Graves' ophthalmopathy or dermopathy.

Thyroid function tests showed high levels of free T4 [7.6 ng/dl (normal 0.9-1.9)] and T3 [516 ng/dl (normal 90-180)] with a suppressed TSH level [<0.1 mIU/L (normal 0.5-4.0)]. TRAb activity was strongly positive [83.2% (normal 0 ± 15)].

An ultrasound study showed diffuse hypertrophy of the thyroid gland and a solitary nodule in the right lobe (Fig. 1). A thyroid scan, performed 30 min after an intravenous administration of Tc-99m pertechnetate, showed diffusely increased uptake in both lobes of the enlarged gland, and further increased uptake in accordance with the solitary right thyroid nodule (Fig. 2). The total thyroid uptake was increased to 9.35 % (normal 0.4-2.5%). Histological examination of the right lobe nodule determined by needle biopsy indicated thyroid follicular adenoma (Fig. 3). Based on these findings, a diagnosis of the coexistence of Graves' disease and AFTN was made.

The treatment was started with Methymazole (MMI) 30 mg daily, and the patient was euthyroid by the end of August, 1994. At that time, a repeat thyroid scan still showed a high uptake (8.79%), and revealed relatively decreased uptake in the
right lobe nodule (Fig. 4A). Her serum free T4 and TSH concentrations were 0.70 ng/dl and 7.0 µU/ml, respectively and TRAb activity was 54%. A T3 suppression with 75 µg of T3 daily for 7 days was then performed. Thyroid uptake after the administration of T3 did not change (8.83%), but the imaging revealed that the Tc-99m uptake in the nodule was slightly suppressed by T3 (Fig. 4B), showing its TSH dependency.

The doses of MMI were tapered off and subtotal thyroidectomy was performed in March, 1995. Total RNA was extracted from both nodular and extra-nodular tissues obtained at the time of the operation. From the analysis of the direct sequence of the polymerase chain reaction products in these thyroid tissues [1], no mutation of the TSH receptor was identified in nucleotides 1894-2037 [2], the mutational hot spots of the third cytoplasmic loop or the sixth transmembrane segment, in both tissues. The patient was subsequently maintained in a euthyroid state with negative TRAb activity.

Discussion

There have been several reports concerning cases of Graves’ disease following AFTN [3-7]. In these cases, it is speculated that the responsiveness of the paranodular normal thyroid tissues was suppressed by short-loop feedback of excess thyroid hormones derived from AFTN [7].

On the other hand, cool or cold solitary thyroid nodules in patients with Graves’ disease sometimes indicate relatively increased iodide uptake compared with paranodular tissues after radioiodine therapy [8, 9] or antithyroid drug treatment [10]. In the thyroid scan, nodules initially appear hypofunctioning because of their inability to trap as much radioiodine as the paranodular tissues. This condition has been defined as the Marine-Lenhart syndrome which is a variant of Graves’ disease with the following criteria: 1) the thyroid scan shows an enlarged gland and one or two poorly functioning nodules; 2) the nodule is TSH dependent and the paranodular tissue is TSH independent; 3) following endogenous or exogenous TSH stimulation, the return of function in the nodule can be demonstrated; and 4) the nodule is benign histologically [9]. It is conceivable that the hot nodule in the present case was functionally suppressed after the administration of T3 due to its dependence on TSH.

It is of interest that the hot nodule in the present case became relatively hypofunctioning compared with extranodular tissues after MMI treatment as reported previously [11]. Uneven distribution of MMI between nodular and extranodular tissues may explain this phenomenon as due to the greater blood flow in the nodule than that in non-nodular thyroid tissues [12]. The nodule might be more sensitive to MMI than extranodular tissues although the in vivo pharmacokinetics of AFTN and Graves’ disease in the same patient as in the present case would be complex. Radioiodine scintigraphy might have been useful in evaluating the pathophysiology in more detail in the present patient [13].

From consecutive thyroid function tests and Tc-99m thyroid scans, it is probable that the present case initially had thyrotoxicosis due to both Graves’ disease and AFTN, and to our knowledge, there have been no reports of the simultaneous coexistence of Graves’ disease and AFTN so far. It is possible that TRAb also affected the function of the nodule before the treatment, but the tumor lost its autonomy during MMI treatment and showed TSH dependency. It is therefore concluded that the patient had a coexisting functioning adenoma with Graves’ disease (Marine-Lenhart syndrome) showing unusual scintigraphic changes unlike its natural course as mentioned above.

Regarding the pathogenesis of AFTN,
constitutively activating mutations in the TSH receptor have recently been reported [14–16]. In the present case, however, no oncogenic mutations of the TSH receptor in the mutational hot spots was identified as in a recent report from Japan [17]. The oncogenic TSH receptor mutations may play a less important role in the pathogenesis of AFTN in an iodine sufficient area like Japan [17].

In summary, we have reported that two distinct thyroid diseases, Graves' disease and AFTN, could cause hyperthyroidism in the same patient. Repeated Tc-99m pertechnetate thyroid scans were helpful in evaluating the reaction of MMI and TSH in both lesions separately in the present case.

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References