

## CASE REPORT

## COEXISTENCE OF GRAVES' DISEASE AND TOXIC ADENOMA: A RARE PRESENTATION OF MARINE-LENHART SYNDROME

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Both Graves' disease and Toxic Nodules cause thyrotoxicosis, albeit by different mechanisms. Their coexistence is called Marine-Lenhart syndrome, the prevalence of which has been reported 2.7–4.1%. In many cases with Marine Lenhart syndrome Graves' disease is accompanied by multiple hyper-functioning nodules, although it is accompanied by a solitary hyper-functioning nodule in rare cases. We here in reported a rare presentation of Marine Lenhart syndrome and its treatment.

**Keywords:** Graves' disease, toxic nodule, Marine-Lenhart syndrome, radioactive iodine, treatment

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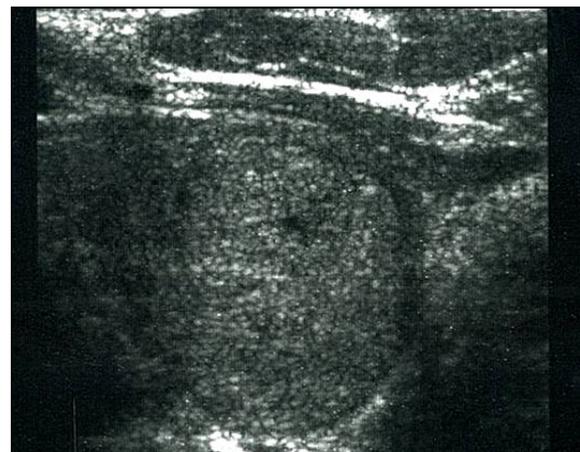
## INTRODUCTION

Graves' disease is characterized by serum antibodies against thyroidperoxidase, thyroglobulin, and the thyroid-stimulating hormone (TSH) receptor. T-cell-mediated autoimmunity can also be demonstrated against the three primary thyroid antigens.<sup>1</sup> Particularly, stimulating antibodies connected to TSH receptors chronically stimulate thyroid gland, leading to hyperthyroidism. Toxic adenoma is a result of several somatic point mutations in the TSHR gene, commonly in the third trans-membrane loop. These single-nucleotide substitutions cause amino acid changes that lead to constitutive activation of the TSHR in the absence of TSH.<sup>2</sup> By this way, excessive thyroid hormone is produced. Both diseases ultimately cause hyperthyroidism, albeit by different mechanisms. Marine-Lenhart syndrome is a rare combination of these two diseases causing hyperthyroidism. The prevalence of this rare syndrome has been reported 2.7–4.1%.<sup>3,4</sup>

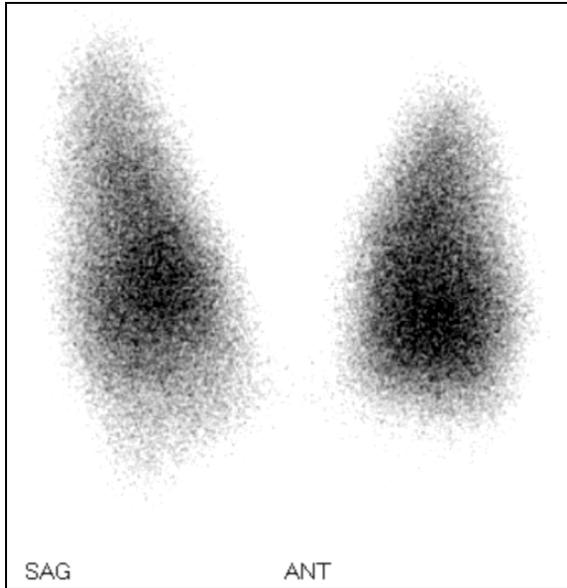
## CASE REPORT

A 46 year-old-man was admitted to the emergency department with the complaint of tremor in his hands, excessive sweating, palpitation, and weight loss (approximately 10 kg for the last three months). In physical examination the thyroid gland was normal sized, while a nodule of 25×25 mm was palpated at the left side of the gland. There were no signs or symptoms consistent with Graves' ophthalmo-pathy or dermopathy. Thyroid hormones were quite high (fT4: 4.45 (0.71–1.85) ng/dL and fT3:24.4 (1.71–3.71) pg/mL) and TSH was suppressed [0.0006 (0.35–4.94)  $\mu$ U /mL] in laboratory analysis. Antithyroglobulin (anti-TG) antibodies were negative, while antithyroid peroxidase (anti-TPO) and TSH receptor antibodies were positive [424 (0–35) IU/ml and 142 (0–10) U/L, respectively]. A thyroid ultrasonography revealed a heterogeneous parenchyma and increased vascularization. In addition, inferior portion of the left lobe contained an iso-echoic nodule of a diameter of

25×25 mm, which contained degenerative cystic areas (Figure-1). A thyroid scintigraphy performed 30 min after intravenous administration of Tc-99m pertechnetate showed a significant amount of almost homogeneous radiotracer uptake in both lobes. The lower part of the left lobe was characterized by an increased uptake (toxic adenomas) (Figure-2). Cytopathology of fine-needle aspiration biopsy was consistent with a colloid nodule. An initial treatment consisting of methimazole 30 mg and propranolol 80 mg was begun. The dosing of the drugs was adjusted on a monthly basis and clinical and biochemical euthyroidism was achieved at the end of the third month. The patient was administered 16 mCi radioactive iodine. TSH was 8.3 $\mu$ U/mL, fT4 was 0.96 ng/ dL and fT3 was 2.3 pg/mL and levothyroxine 50 mcg was started at the follow-up 1 month later. TSH was 2.1  $\mu$ U /mL and fT4 was 1.3 ng/dL at the follow-up two months later. At six month follow-up the patient was still in euthyroid state while taking levothyroxine 50 mcg.



**Figure-1: An isoechoic nodule of a diameter of 25×25 mm with cystic degenerative areas and a peripheral hypoechoic halo in inferior portion of the left lobe**



**Figure-2: A thyroid scintigraphy performed 30 min after intravenous administration of Tc-99m pertechnetate showed a significant amount of almost homogeneous radiotracer uptake in both lobes. An even more increased uptake is observed at the region corresponding to the nodule region on ultrasonography.**

## DISCUSSION

Previous studies have reported that thyroid nodules accompany Graves' disease at varying rates between 25–30% (5–7). The majority (>95%) of these nodules are hypo-functioning, while a small minority is hyper-functioning nodules.<sup>8</sup> Coexisting Graves' disease and functional nodules are known as Marine-Lenhart syndrome.<sup>9,10</sup> In many cases with Marine-Lenhart syndrome Graves' disease is accompanied by multiple hyperfunctioning nodules, although it is rarely accompanied by a solitary hyper-functioning nodule, as in our case.

Marine-Lenhart syndrome is diagnosed with scintigraphic imaging. Diffusely increased uptake and an even more uptake at the region of a sonographically detected nodule are characteristic features of scintigraphy. Accompanying toxic nodules should always be considered as a possibility and scintigraphic images be reviewed especially in resistant or frequently recurring cases. It has been reported in literature that thyroid papillary carcinoma is rarely detected in toxic nodules of patients with Marine-Lenhart syndrome.<sup>11</sup> Hence, it is reasonable to perform a fine needle aspiration biopsy and determine the nodule's histology since the treatment must be thyroidectomy, should a malignancy be present.

The first step in therapy is anti-thyroid drug therapy. Although an initial resistance to anti-thyroid

drug therapy may be observed, thyrotoxicosis can be usually controlled thereafter. However, a complete cure seems unachievable with anti-thyroid drug therapy alone since recurrences frequently occur upon dose decrements or quitting drug therapy. Other options are thyroidectomy and radioactive iodine therapy. It has been reported in literature that Marine-Lenhart syndrome has a relatively greater mean radioactive iodine requirement and is more resistant to radioactive iodine than diffuse toxic goitre.<sup>4</sup> This may indeed be true for patients with Graves' disease with multiple toxic nodules, because the required amount of radioactive iodine will increase with increasing number of nodules. Furthermore, the treatment becomes even more complicated given the difficulties with dose adjustments of radioactive iodine. Hence, radioactive iodine therapy may not be appropriate for patients with multiple nodules, owing to difficulties in dose adjustment and increased possibility of side effects with dose increments. In the light of the above information, thyroidectomy seems more reasonable for the therapy of multiple toxic nodules accompanying Graves' disease. Likewise, Cakir preferred subtotal thyroidectomy owing to the possibility of increased dose requirement for radioactive iodine with multiple toxic nodules. Similarly, the malignant potential of multiple nodules may be a second incentive for surgery.<sup>10</sup>

As for solitary toxic nodules accompanying Graves' disease, on the other hand, we believe that radioactive iodine therapy should be the first option in nodules proven to be benign since dose adjustment and therapy with low dose radioactive iodine are possible in such cases. Likewise, we achieved a successful outcome with low dose radioactive iodine in our case.

## CONCLUSION

Clinicians and nuclear medicine specialists should be very careful while examining thyroid scintigraphy images of patients considered having Graves' disease. The possibility of coexisting toxic nodules should be remembered particularly in cases with Graves' disease requiring high dose anti-thyroid drugs. Presence of toxic nodule completely changes the treatment plan. We suggest that radioactive iodine treatment is appropriate in patients with Marine-Lenhart syndrome with a single nodule.

## REFERENCES

1. Rapaport B, McLachlan SM. Thyroid autoimmunity. *J Clin Invest* 2001;108(9):1253–9.
2. Tonacchera M, Agretti P, Rosellini V, Ceccarini G, Perri A, Zampolli M, *et al.* Sporadic non autoimmune congenital hyperthyroidism due to a strong activating mutation of the thyrotropin receptor gene. *Thyroid* 2000;10(10):859–63.

3. Carnell NE, Valente WA. Thyroid nodules in Graves' disease: classification, characterization and response to treatment. *Thyroid* 1998;8(8):647–52.
4. Charkes ND. Graves' disease with functioning nodules (Marine-Lenhart syndrome). *J Nucl Med* 1972;13(12):885–92.
5. Kim WB, Han SM, Kim TY, Nam-Goong IS, Gong G, Lee HK, *et al.* Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. *Clin Endocrinol (oxf)* 2004;60:719–25.
6. Gerenova J, Buysschaert M, deBurbure CY, Daumerie C. Prevalance of thyroid cancer in Graves' disease: a retrospective study of a cohort of 103 patients treated surgically. *Eur J Intern Med* 2003;14(5):321–5.
7. Mishra A, Mishra SK. Thyroid nodules in Graves' disease: implications in an endemically iodine defficient area. *J Postgrad Med* 2001;47(4):244–7.
8. Cakir M. Marine-Lenhart syndrome. *J Natl Med Assoc* 2005;97:1036–8.
9. Braga-Basaria M, Basaria S. Marine-Lenhart syndrome. *Thyroid* 2003;13(10):991.
10. Cakir M. Diagnosis of Marine-Lenhart syndrome. *Thyroid* 2004;14(7):555.
11. Scherer T, Wohlschlaeger-Krenn E, Bayerle-Eder M, Passler C, Reiner-Concin A, Krebs M, *et al.* A case of simultaneous occurrence of Marine-Lenhart syndrome and a papillary thyroid microcarcinoma. *BMC Endocr Disord* 2013;13:16.

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