Rare Presentation of Marine-Lenhart Syndrome

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Abstract: The combination of autoimmune Graves' disease with a solitary hot thyroid nodule suppressing the remainder of the thyroid gland is rare. We report a case of Graves' disease associated with a single hyperfunctioning nodule with suppression of the remaining gland.

A 45 year old male patient with past medical history of autoimmune Graves' disease with severe ophthalmopathy was referred to endocrine clinic. His symptoms started with dry eyes several years ago without associated hypermetabolic symptoms. Further investigation revealed hyperthyroidism; he was started on methimazole. Thyroid stimulating immunoglobulin was 484 %(reference: <140%, Method: immunoassay). Thyroid scan with I-123 sodium iodide showed uptake of 28.3 percent at 24 hours, and showed a large area of intense activity mid and lower left thyroid lobe with suppression of uptake in the rest of the thyroid gland. Thyroid ultrasound showed a heterogeneous well-defined 1.3x1.0x1.0 cm left mid lower pole nodule. These findings are suggestive of a rare variant of Marine-Lenhart syndrome.

Graves' hyperthyroidism is thought to be caused by autoantibodies stimulating the TSH receptors. Thyroid nodules associated with Graves' disease have been reported with the incidence between 25 to 30%, most of which are cold nodules. The incidence of Graves' disease accompanied by hot nodules ranges from 2.7 to 4.1%.These rare cases of Graves' disease with accompanying functioning thyroid nodules are known as Marine-Lenhart syndrome. Most reported cases of Marine-Lenhart syndrome are Graves' disease with multiple hyperfunctioning nodules. Our case represents an unusual variety in which Graves' disease with a hyperfunctioning solitary nodule was associated with suppression of the remaining gland. Acquired mutations resulting in constitutively activated TSH receptors and the presence of anti TSH receptor autoantibodies might be responsible for the development of Marine-Lenhart syndrome.

Keywords: Marine-Lenhart, autoimmune, Graves' disease, solitary thyroid nodule.

BACKGROUND

While thyroid nodules are encountered in 25-30% of patients with Graves' disease, the vast majority of these nodules are non-functional. A tiny fraction of these nodules may be hyperfunctioning; this rare combination is referred to as *Marine-Lenhart Syndrome* [1]. A still rarer presentation of this syndrome is seen in those patients with coexistent Graves' disease with a single, rather than multiple hyperfunctioning (hot) nodule(s). Unless such hyperfunctioning nodules are biopsied or surgically removed, it is unclear if these nodules represent a localized form of autoimmune Graves' disease, an acquired, localized, mutation of the TSH receptor gene resulting in constitutive activation of the TSH receptor with development of a toxic adenoma or adenomatous hyperplasia, or Graves' disease combined with hemiagenesis of the thyroid. In a recent series of 468 patients with Graves' disease from the University of Maryland [2], 12.8% had nodules, 5.8% had single hypofunctional nodules, 4.5% had multiple nodules, only 1% had Graves' disease presenting as a single autonomous nodule, 1.7% had "patchy" (localized areas of) Graves' disease, 1.3% had thyroid cancer. Based on fine needle aspiration biopsy (FNAB), surgical pathology, or response to treatment, the remaining patients had pseudo-nodules of autoimmune thyroid disease, autonomous nodules (Marine-Lenhart syndrome), hyperplastic adenomas, colloid goiter, or Hashitoxicosis [transient episodes of hyperthyroidism occurring in patients with autoimmune thyroiditis in which the autoimmune, cytotoxic, inflammatory process results in sudden release of pre-formed thyroid hormone from damaged follicles]. Prior to this report, only 4 cases of solitary hot nodules in Graves' disease patients had been reported [3].

CASE REPORT

Our patient is a 45 year old man with Graves' disease with exophthalmos for 3 years who was referred to endocrine clinic for further evaluation. His symptoms started with dry eyes several years ago without associated hypermetabolic symptoms such as weight loss, hair loss, hyperdefecation, palpitations, anxiety, sleep disturbance or heat intolerance. The patient smoked about 7 pack years and quit 10 years ago. He doesn't drink alcohol. He doesn't have a family history of thyroid disease. He takes methimazole for hyperthyroidism and artificial tears for eye symptoms. He uses sunglasses with ultraviolet B protection on sunny days.

On physical examination, blood pressure was 115/66 mm Hg, pulse 92 bpm, BMI was 26 kg/m^2. He was a healthy looking man, not in any distress. He had

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prominent exophthalmos with bilateral lid lag. The thyroid gland was not palpable. The lungs were clear to auscultation. Auscultation of the heart revealed a normal rate and rhythm, normal S1 and S2 without any murmur, rubs or gallops. Abdomen was benign; extremities were warm and diaphoretic with bilateral 2+ dorsalis pedis pulses.

Laboratory studies when he was seen in the clinic revealed TSH by chemiluminescence= 0.01 mIU/L (range: 0.40-4.50 mIU/L), Triiodothyronine level by immunoassay =1.26 ng/ml (126.39 ng/dL, conversion factor: 0.01, (range: 0.60-1.81 ng/ml)), thyroxine level by immunoassay= 113.26 nmol/L (8.8 ug/dL, conversion factor: 12.87 (range: 57.9-140.3 nmol/L)), T3 resin uptake by spectrophotometry= 38.12%. Thyroid stimulating immunoglobulin was 484 %(reference: <140%, Method: immunoassay). Thyroid scan with I-123 sodium iodide showed uptake of 28.3 percent at 24 hours, and showed a large area of intense activity mid and lower left thyroid lobe with suppression of uptake in the rest of the thyroid gland (Figure **1**). Thyroid ultrasound showed a heterogeneous, well-defined 1.3x1.0x1.0 cm left mid lower pole nodule (Figure **2**).

DISCUSSION

Graves' hyperthyroidism is believed to be caused by autoantibodies stimulating the TSH receptors [4, 5]. Most thyroid nodules associated with Graves' disease are cold nodules, whose incidence ranges from 25 to 30% [1], whereas hot nodules associated with Graves' disease have an incidence of 2.7 to 4.1%, most of which are multiple hot nodules [2, 6]. Graves' disease associated with single hot nodules is even rarer, with only 4 reported cases so far [2, 3]. These cases of Graves' disease with accompanying functioning thyroid nodules are known Marine-Lenhart syndrome [7, 8]. Our patient represents the most unusual variety in which Graves' disease with a solitary hyperfunctioning nodule was associated with suppression of the remaining gland.

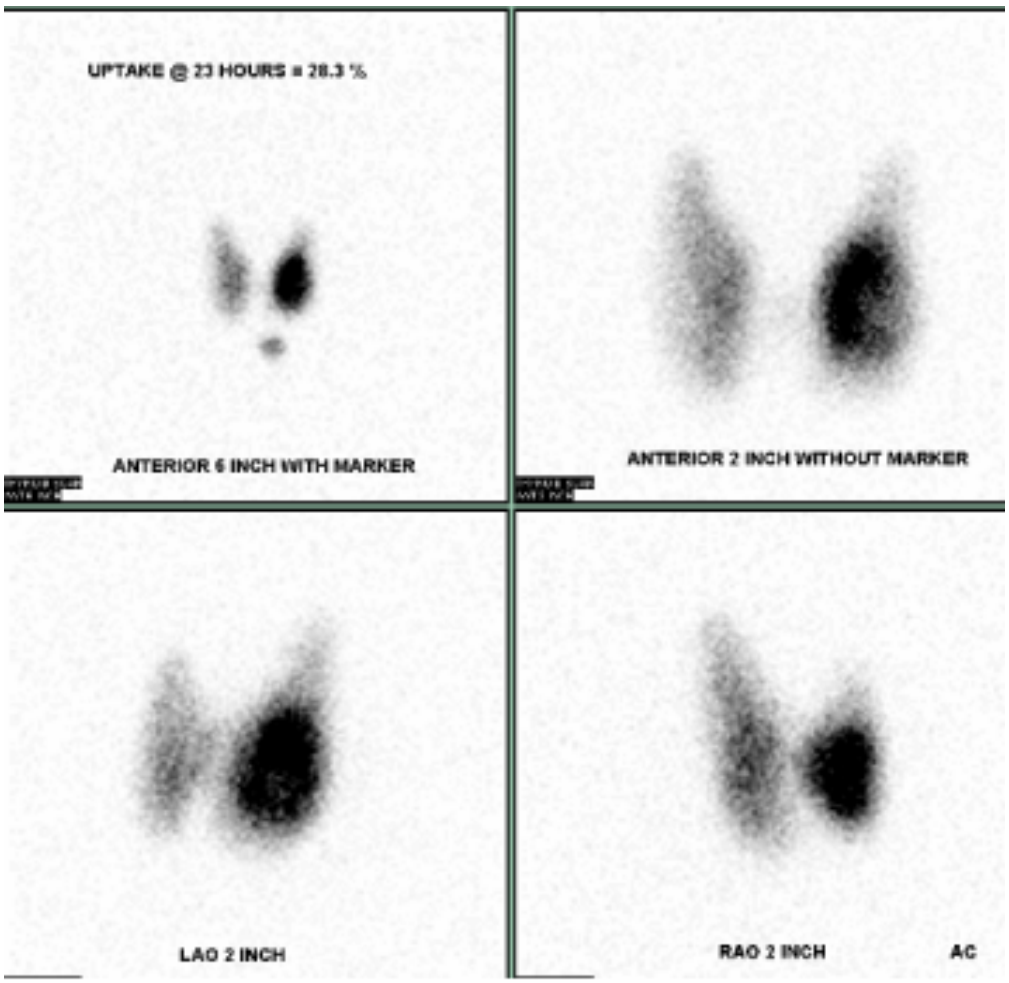

Figure 1: I 123 sodium iodide scan of thyroid gland showing hot nodule in the left lobe suppressing the remainder of the gland.

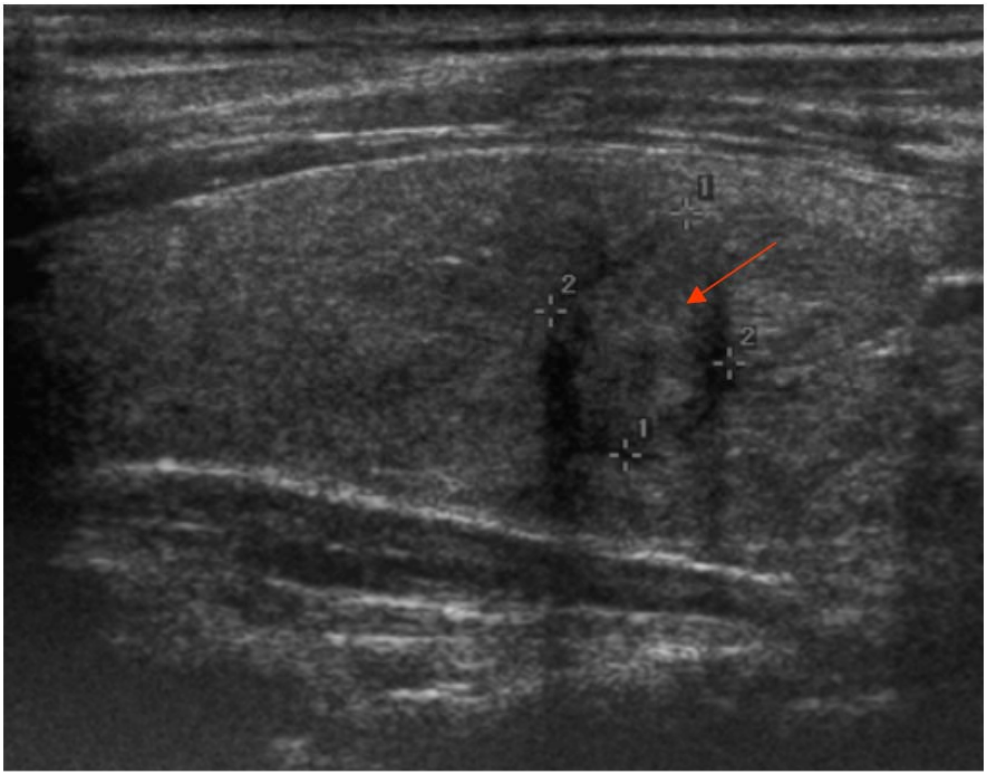

Figure 2: Ultrasound of thyroid showing nodule in left lobe with a nearly complete halo.

The pathophysiology of Marine-Lenhart syndrome remains unclear. Acquired mutations resulting in constitutively activated TSH receptors and the presence of localized rather than generalized anti- TSH receptor autoantibodies might be responsible for the development of Marine-Lenhart syndrome [9]. Case reports have been published suggesting possible development of hyperfunctioning nodules in Graves' disease after ablative treatment with Iodine 131 [10]. One report of Marine-Lenhart syndrome described a patient with a hot nodule containing papillary thyroid microcarcinoma, which upon total thyroidectomy revealed bilobar involvement, prompting the authors to suggest that fine needle aspiration biopsy should not be restricted to cold nodules [11]. While cigarette smoking is a known trigger factor for Graves' disease and, in particular, Graves' opthalmopathy [12], it is interesting that in this patient the history of cigarette smoking preceded the clinical onset of Graves' disease by about 10 years.

CONCLUSION

While thyroid nodules are relatively common in patients with autoimmune Graves' disease, hyperfunctioning nodules with Graves' disease (Marine-Lenhart syndrome) are very rare and single hyperfunctional nodules in Graves' disease are rarer still. Such hyperfunctional nodules are more easily detected either before Graves' disease is apparent or after it goes into remission. Precise characterization of such nodules may require surgical or fine needle biopsy or observation of response to therapy. Routine measurement of Thyroid Stimulating Immunoglobulin in hyperthyroid patients with toxic uninodular or multinodular goiter may improve the diagnostic yield. Conversely hyperfunctioning nodules in Graves' disease patients may not be apparent until a pre-I131 therapy thyroid scan is performed.

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