

**CASE REPORT**

# A new case of Marine-Lenhart syndrome with a papillary thyroid carcinoma

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**Key Clinical Message**

We report the case of a patient with the coexistence of Graves' disease and autonomously functioning thyroid nodules. Because of the suspicious ultrasound pattern, he was submitted to fine-needle aspiration of the hot nodule and cytology revealed a papillary thyroid cancer. After total thyroidectomy a papillary thyroid cancer was found.

**KEYWORDS**

Graves' disease, hot thyroid nodule, Marine-Lenhart syndrome, thyroid cancer

## 1 | INTRODUCTION

Graves's disease is an autoimmune form of hyperthyroidism, caused by thyroid stimulating hormone receptor antibodies (TRAb). Thyroid nodules occur in 10%-35% of patients with Graves' disease.<sup>1</sup> The majority of these nodules are hypo-functioning; hot nodules have been reported with an incidence of 2.7%-4.1% in Graves' disease and most of them are multiple hot nodules. Single hot nodules are even rarer with only few reported cases.<sup>1</sup> The coexistence of Graves' disease and autonomously functioning thyroid nodules (AFTN) is known as Marine-Lenhart syndrome (MLS).<sup>2</sup> It has a prevalence of 0.8%-2.7% among patients with Graves' disease,<sup>1</sup> and it is diagnosed with scintigraphic imaging demonstrating a diffusely increased uptake of thyroid gland together with an even greater uptake in the region of a sonographically detected nodule. In this case, the two disease entities develop in the same patient, but independent from each other and it should be considered differently from patients with toxic adenoma who develop Graves' disease after 131-I therapy.<sup>2</sup> Unless such nodules are biopsied or surgically removed, it remains unclear if these nodules represent a localized form of autoimmune Graves' disease or an acquired, localized mutation of the TSH receptor gene, resulting in constitutive activation of TSH receptor, with development of a toxic adenoma.

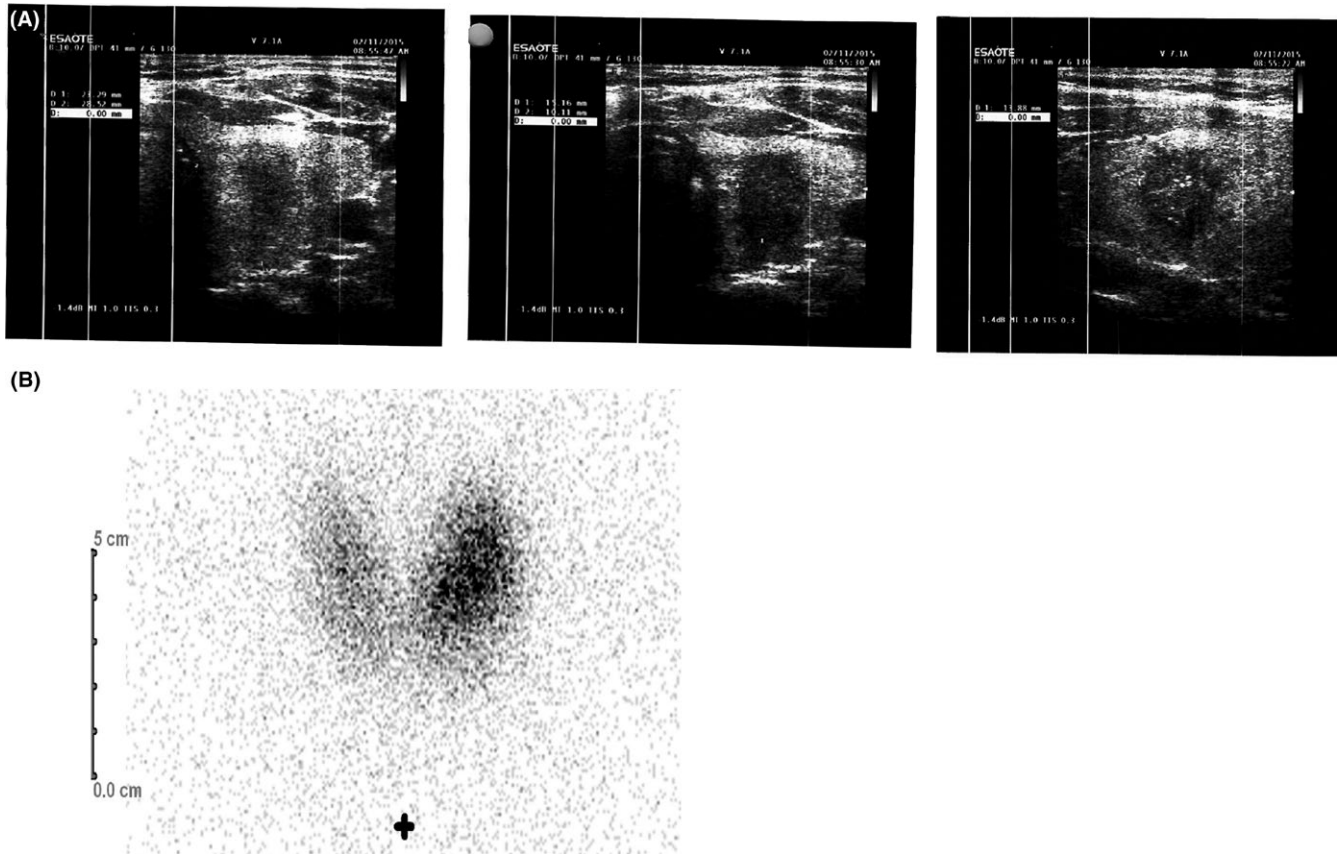
## 2 | CLINICAL CASE

In March 2014, a 34-year-old man sought medical advice because of palpitation, asthenia, and weight loss. Thyroid function tests revealed hyperthyroidism (TSH 0.03 mcUI/mL (NV 0.4-4), fT4 26.6 pg/mL (NV 10.6-19.4), fT3 8 pg/mL (NV 4-8.3), and methimazole was started.

He came to our attention a year later on 5 mg methimazole twice daily, showing euthyroidism (TSH 1.1 mcUI/mL, fT4 16.9 pg/mL, fT3 5.1 pg/mL). At that time, TRAb were negative and thyroid ultrasound showed a modestly enlarged, slightly hypoechoic thyroid gland with a hypoechoic, hypervascularized nodule of 15 × 10 × 14 mm, in the middle of the left thyroid lobe. A <sup>99</sup>Techneium thyroid nuclear scan showed a hot area in the middle of the left thyroid lobe, compatible with the hypoechoic lesion discovered at ultrasonography, with a suppressed uptake of the remaining thyroid tissue.

A diagnosis of toxic adenoma was made, 10 mg-methimazole therapy continued and 131-I radiometabolic treatment was planned.

In November 2015, after a week discontinuation of methimazole therapy, he was admitted to the Endocrinology Department of Pisa University to receive 131-I radiometabolic treatment. He showed the following thyroid function: TSH 0.35 mcUI/mL, fT4 1.46 ng/dL, fT3 4.5 pg/mL,



**FIGURE 1** A, Thyroid ultrasound showing a hypoechoic nodule in the left lobe with internal microcalcifications. B,  $^{131}\text{I}$  scan with a predominant uptake in the middle left thyroid lobe in correspondence of the thyroid nodule

ioduria  $<25 \mu\text{g/L}$  ( $<300$ ), negative thyroglobulin, and thyroid peroxidase autoantibodies. However, at that time, he presented positive TRAb (1.86 UI/L NV  $<1.5$ ) with a light bilateral exophthalmos, although without signs of active ophthalmopathy.

Thyroid ultrasound demonstrated an enlarged (31.3 mL) hypoechoic hypervascularized gland with a dimensionally stable solid hypoechoic left nodule, with internal microcalcification (Figure 1A). At that time thyroid  $^{131}\text{I}$  scan revealed an inhomogeneous increased diffuse uptake (3-hours uptake 24.7%, 24 hours 46.7%) with a predominant uptake in the middle left thyroid lobe, in correspondence of the known thyroid nodule (Figure 1B).

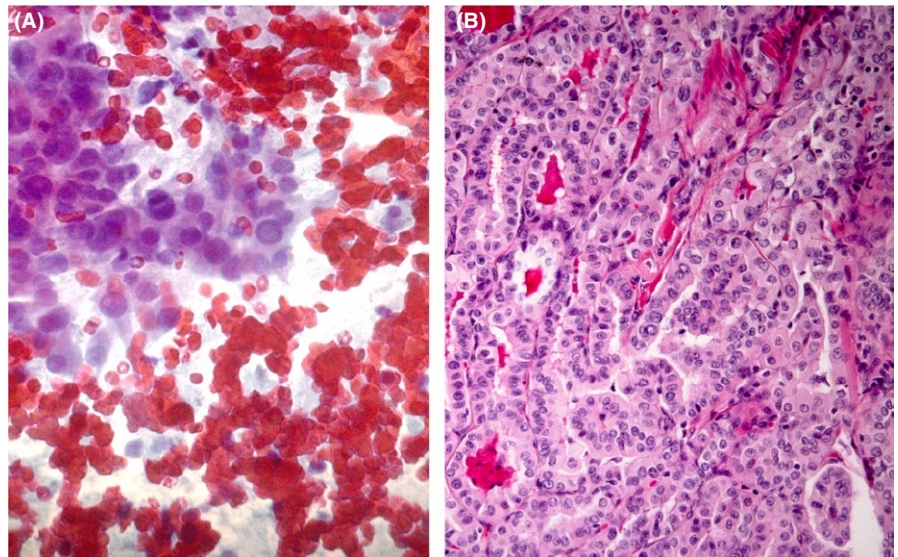
Thus, clinical, biochemical and nuclear signs were consistent with Graves' disease associated with an autonomous left thyroid nodule, suggesting a MLS diagnosis.

Before the radioiodine treatment, because of the suspicious ultrasound pattern, he was submitted to a fine-needle aspiration of the left nodule and cytology revealed a papillary thyroid cancer (Figure 2A).

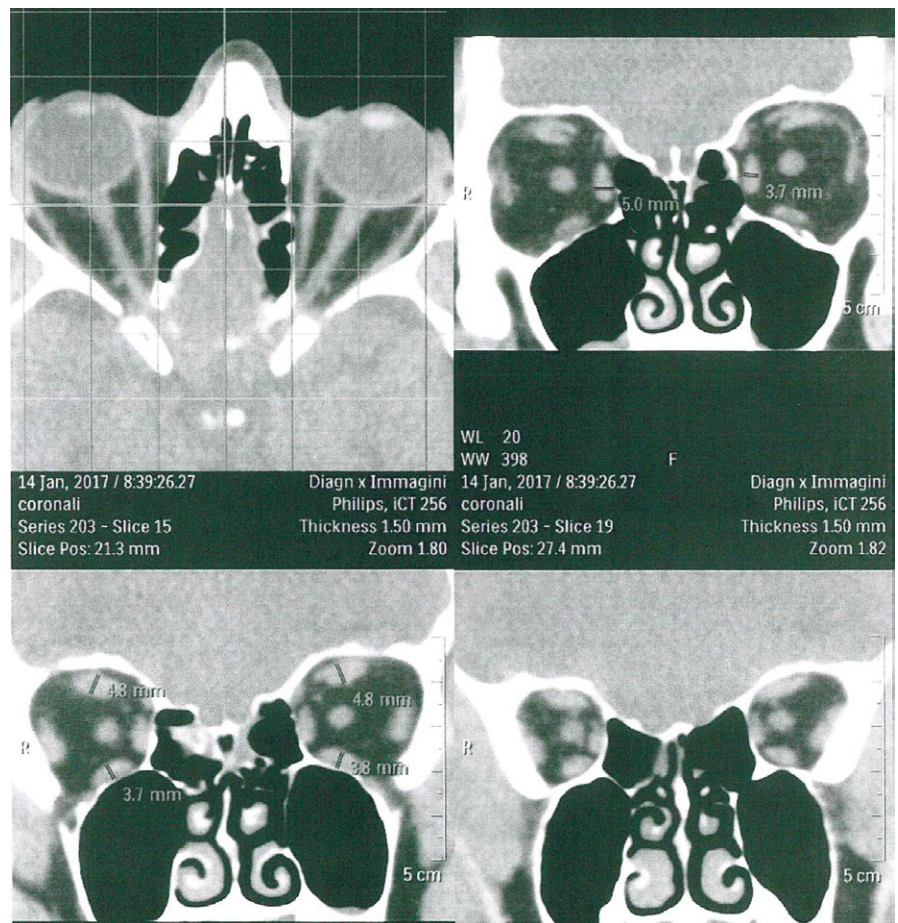
In February 2016, the patient was submitted to total thyroidectomy that confirmed a papillary thyroid cancer (15 mm), classic variant with a 30% tall cell, infiltrating

peri-thyroid tissues, in diffuse goiter (pT3NxMx) (Figure 2B). Furthermore, the carcinoma section showed a mutation of BRAF V600E and analysis of TSH receptor gene did not show any mutation.

Due to the high-risk histology, he started levothyroxine suppressive therapy and in May 2016, after recombinant TSH stimulation, he was submitted to thyroid remnant ablation with 100 mCi  $^{131}\text{I}$ . Steroid treatment was associated to prevent ophthalmopathy worsening. Thyroglobulin after TSH stimulation (TSH 116 mcUI/mL) was 0.36 ng/mL with negative antithyroglobuline antibodies. Postdose whole body scan demonstrated an anterior cervical uptake, due to thyroid remnant with no other pathological uptakes, while cervical ultrasound did not show any cervical pathological remnant or lymphadenopathy. He is now kept on suppressive levothyroxine therapy, and he is undergoing clinical, biochemical, and ultrasound follow-up. In the last months, he complained a worsening exophthalmos, although with weak activity signs. He has been submitted to an orbit CT that confirmed the bilateral exophthalmos and a thickening of the rectus muscles (Figure 3). Due to the low active ophthalmopathy at the moment he has not been submitted to specific therapy, expect for artificial tears.



**FIGURE 2** A, Cytological examination of the left thyroid nodule suspicious for papillary thyroid cancer. B, Histologic examination of left thyroid nodule confirming the presence of a papillary thyroid cancer



**FIGURE 3** Orbit CT scan showing bilateral exophthalmos and tickening of the rectus muscles

### 3 | DISCUSSION

This patient presented the rare MLS associated with an even more special occurrence of a BRAF mutated papillary thyroid cancer within a hot nodule.

Intranodular thyroid carcinoma in hyper-functioning thyroid nodules is so rare that the main international

guidelines do not suggest cytological evaluation of hot nodules.<sup>3,4</sup> However, a quite recent review reported a 3.1% prevalence of thyroid carcinoma in hyper-functioning nodules submitted to thyroid surgery.<sup>5</sup> On the other hand, it is still matter of debate whether the frequency of thyroid cancer is higher in patients with Graves' disease. The prevalence of palpable nodules is higher in these patients than

**TABLE 1** Ultrasound suspicious characteristics, according to ETA guidelines 2017<sup>5</sup>

US suspicious features
Solid pattern
Nonoval shape
Irregular margins
Microcalcifications
Markerd hypoechogenicity
Suspicious local lymphadenopathy
Extrathyroidal extension
Absent halo
Type III vascularity at Doppler US (still controversial)

in general population, while the prevalence of concomitant thyroid carcinoma and Graves' disease has been reported to be from 1.1% to 7.1%, although the majority of these malignancies arise from cold nodules.<sup>4</sup> Moreover, thyroid cancer in Graves' patients could be more aggressive, growing more invasively and developing more lymph node and distant metastases than in euthyroid controls.<sup>4</sup> However, other studies did not confirm these data and at the moment, carcinoma in Graves' disease should be treated like in general population.

Anyway, ultrasound aspects should be always deeply considered even in Graves' disease patients, evaluating the eventual suspicious US findings as suggested in the recent ETA guidelines<sup>5</sup> in order to evaluate the opportunity to propose FNA even in some hot nodules (Table 1).

The reported cases of MLS are few and generally benign. The case of malignancy associated with MLS is really a rare event. To our knowledge, up to now there are only seven other similar cases reported in the literature and only one of them showed a BRAF V600E mutation.<sup>6</sup>

Thus, although routinely cytological investigation of hyper-functioning nodules it is not recommended, our case report suggests that it is reasonable to carefully evaluate AFTN that has clinical and sonographic suspicious features, especially before radioactive iodine treatment. Hyper-functioning state does not definitely exclude the possibility of an intranodular malignancy and fine needle aspiration should be consider in suspicious nodules.


## AUTHORSHIP

ML: clinician who followed the patient. MT: clinician who performed laboratory investigations and wrote the manuscript. EM: clinician who followed the patients and wrote the manuscript.

## CONFLICT OF INTEREST

None declared.

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