CASE REPORT



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A Case of simultaneous occurrence of Marine – Lenhart syndrome and a papillary thyroid microcarcinoma

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Abstract

Background: Marine-Lenhart syndrome is defined as the co-occurrence of Graves' disease and functional nodules. The vast majority of autonomous adenomas are benign, whereas functional thyroid carcinomas are considered to be rare. Here, we describe a case of simultaneous occurrence of Marine-Lenhart syndrome and a papillary microcarcinoma embedded in a functional nodule.

Case presentation: A 55 year-old, caucasian man presented with overt hyperthyroidism (thyrotropin (TSH) <0.01 μ IU/L; free thyroxine (FT4) 3.03 ng/dL), negative thyroid peroxidase and thyroglobulin autoantibodies, but elevated thyroid stimulating hormone receptor antibodies (TSH-RAb 2.6 IU/L). Ultrasound showed a highly vascularized hypoechoic nodule (1.1 × 0.9 × 2 cm) in the right lobe, which projected onto a hot area detected in the ^{99m}technetium thyroid nuclear scan. Overall uptake was increased (4.29%), while the left lobe showed lower tracer uptake with no visible background-activity, supporting the notion that both Graves' disease and a toxic adenoma were present. After normal thyroid function was reinstalled with methimazole, the patient underwent thyroidectomy. Histological work up revealed a unifocal papillary microcarcinoma (9 mm, pT1a, R0), positively tested for the BRAF V600E mutation, embedded into the hyperfunctional nodular goiter.

Conclusions: Neither the finding of an autonomously functioning thyroid nodule nor the presence of Graves' disease rule out papillary thyroid carcinoma.

Keywords: Toxic adenoma, Graves' disease, Marine-Lenhart syndrome, Papillary carcinoma, Hyperthyroidism

Background

The eponym Marine-Lenhart syndrome is typically used for the rare condition of concurrent manifestation of Graves' disease and thyroid autonomy (Plummer's disease) [1-3]. In general, the majority of autonomic adenomas of the thyroid are benign, whereas autonomic thyroid carcinomas are considered a relatively rare finding [4,5]. Here, we report the exceptional case of simultaneous occurrence of Marine-Lenhart syndrome and a papillary microcarcinoma, which was embedded in an autonomous adenoma.

Case presentation

A 55-year-old Caucasian man was referred because of abnormal thyroid function tests and intermittent atrial fibrillation. He reported of occasional palpitations, episodes of tachycardia (up to 200 bpm), especially under exertion, and excessive sweating. The patient was previously started on bisoprolol 2.5 mg once daily and presented with normofrequent sinus rhythm. On physical examination his thyroid was moderately enlarged (WHO grade Ib) and soft. Thyroid function tests revealed hyperthyroidism with complete suppression of thyroid stimulating hormone (TSH) (<0.01 μ IU/mL, see Table 1 for reference range), elevated FT4 (3.03 ng/dL) and increased total thyroxine (TT4) and total triiodo-thyronine (TT3) levels (132 and 2.53 ng/mL respectively). Thyroid peroxidase (TPO) and thyroglobulin



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Timepoint	Intial diagnosis	Follow up 1 (after 3 weeks)	Follow up 2 (after 9 weeks)	Post surgical (after 17 weeks)
FT4 (0.76 – 1.66 ng/dL)	3.03	2.09	1.44	1.27
TSH (0.44 – 3.77 µIU/mL)	<0.01	<0.01	<0.01	7.26
TT4 (58 – 124 ng/mL)	132	109	90	80
TT3 (0.8 – 1.8 ng/mL)	2.53	1.91	1.49	0.89
TgAb (< 33 IU/mL)	<10	ND	ND	<10
TPO (< 28 IU/mL)	9	ND	ND	ND
TSH-RAb (< 1.75 IU/L)	2.6	ND	ND	ND
TBG (14 – 32 μg/mL)	19.7	19	ND	28.7
Tg (1.6 – 55 ng/mL)	ND	ND	ND	5.7
Calcitonin (< 8 pg/mL)	2.7	ND	ND	ND

Table 1 Laboratory values

ND – not determined.

autoantibodies (TgAb) were negative, but TSH-RAbs were elevated (2.6 IU/L), indicating that the patient suffered from Graves' disease (See Table 1). Upon initial admission the patient showed no clinical signs of Graves' orbitopathy. A thyroid ultrasound showed multiple hypoechoic nodules in both thyroid lobes. The most prominent nodule appeared in anterior caudal position of the right lobe embedded in a diffusely heterogeneous thyroid gland. The lesion measured $1.1 \times 0.9 \times 2$ cm, showed no signs of microcalcification, but was highly vascularized in the Doppler color flow, whereas the rest of the thyroid tissue showed moderate signs of hypervascularization (Figure 1). A ^{99m}Technetium thyroid nuclear scan displayed an orthotopic, V-shaped thyroid with asymmetrical uptake and a hot area in the right lower lobe compatible with the hypoechoic, hypervascularized lesion discovered in ultrasonography (Figure 2). Uptake in the remaining thyroid tissue was comparatively lower but not suppressed, with increased overall uptake (4.29%, reference range: 0.5% - 2%) and almost no detectable background activity. Thus, both signs of Graves' disease and thyroid autonomy were coexisting in our patient hence the diagnosis Marine-Lenhart syndrome.

The patient was then started on 20 mg methimazole twice daily for the first seven days after his initial presentation, followed by 20 mg methimazole once daily for the following 8 weeks, which completely resolved his hyperthyroid condition until follow up 2 (Table 1). However, because of the unlikeliness of a permanent remission, the existence of multiple "cold" nodules and the relative resistance of patients with coexisting Graves' disease and toxic adenoma to radioiodine therapy [2], a definitive, surgical treatment was aspired. The patient therefore underwent thyroidectomy three months after initial diagnosis. The patient received alternating 10 mg and 20 mg methimazole once daily until the thyroid gland was removed. After thyroid surgery bisoprolol 2.5 mg once daily was stopped. Notably, embedded in the nodular area of the right thyroid lobe a, macroscopically, white and firm elastic area was discovered, which was diagnosed as a papillary microcarcinoma (5 mm) in an intraoperative frozen section. Histological work-up revealed a unifocal papillary microcarcinoma (9 mm, pT1a, R0) in the right thyroid lobe with signs of a hyperfunctioning nodular goiter (see Figure 3 A and B). Furthermore, the carcinoma sections were positively tested for the BRAF V600E mutation using the ViennaLab BRAF Strip Assay (Vienna, Austria) (Figure 3C). After a short postoperative recovery phase the patient was discharged under levothyroxine therapy.

A postoperative follow up 17 weeks after the initial diagnosis showed subclinical hypothyroidism, which was fixed by adjusting the levothyroxine therapy (Table 1). Notably, the patient developed a moderately active orbitopathy postoperatively, which was treated with IV corticosteroids for 3 months.

Discussion

The BRAF V600E mutation is usually associated with higher malignancy and aggressiveness in papillary thyroid carcinomas [6] and in most cases with typical ultrasound features of thyroid malignancy [7]. However, due to the unifocality of the lesion and the fact that the papillary carcinoma in our patient measured less than 10 mm, according to the 2009 consensus of the American Thyroid Association no radioiodine therapy was performed [8]. Therefore, postsurgical thyroglobulin (TG) levels are still detectable in our patient (Table 1) and only of limited use in postsurgical follow up.

It is commonly believed that papillary microcarcinomas only rarely collocate within toxic thyroid adenomas, although several case reports are found in the literature [9-16]. A selection of retrospective studies estimate the risk of concurrent papillary carcinomas in functioning



nodules ranging from 0.34% up to 5% [5,17,18]. In a cohort of US children with toxic adenoma the malignancy rate was yet higher (about 11%) [19]. Thus, despite the relatively low risk of malignant transformation of functioning nodules, these lesions need careful clinical follow up with ultrasound and possibly fine needle aspiration biopsy especially when patients are young.

Furthermore, it is still subject of debate whether the frequency of thyroid cancer is higher in patients with Graves' disease, mostly because the studies are typically retrospective and extend over a long period of time, where diagnostic capabilities and tools might have changed significantly (extensively reviewed in [20]). However, it seems that the prevalence of palpable nodules is about 3-fold higher in Graves' patients (15.8%) [21] compared to the general population living in a non-endemic region (5%) [22]. Studies relying on ultrasound imaging also find a higher prevalence for thyroid nodules in patients suffering form Graves' disease (33.6%) [23] compared to the general population (about 26%) although to a lesser extent [24,25]. Of note, in the former study more than half the patients suffering from Graves' disease developed thyroid nodules during the 2-year follow up, which suggests that Graves' disease promotes *de novo* thyroid nodule formation [23]. Furthermore, the mean malignancy rate of palpable nodules in Graves' patients is about 16% versus a 5% malignancy rate in the general population (reviewed in [26]). Thus, in conjunction with the above-mentioned prevalence rates of thyroid



nodules, it can be estimated that Graves' patients have an almost 10-fold higher chance of developing thyroid cancer. In a retrospective multicenter study with more than 500 Graves' patients thyroid carcinomas were found in 3.8% (20 out of 21 were papillary carcinomas) [27]. Another study matched these results and found a malignancy rate of 3.3% in their collective of Graves' patients [28], whereas the incidence of thyroid cancer in the general US population was estimated at about 14.4 per 100,000 [29]. Of note, in the former study all papillary carcinomas were detected within thyroid nodules embedded into a Graves' goiter. In total 15% of the patients suffering from both, nodules and



Graves' disease, also had thyroid carcinomas [27]. In another study the risk for malignancy of a thyroid nodule within a toxic diffuse goiter even reached 22% [30], therefore any nodule within a Graves' goiter should be carefully examined to rule out a thyroid carcinoma.

There is evidence that thyroid cancer in Graves' patients is more aggressive. Therefore, an important question is, whether the presence of Graves' disease in thyroid cancer patients affects their clinical outcome. Studies have found that in Graves' patients thyroid carcinomas grow more invasively and develop lymph node and distant metastases more frequently compared to euthyroid controls [31-33], although a more recent study was not able to confirm these data [34]. Yet, given the possibility that Graves' disease increases nodule formation and their respective risk for malignant transformation, it is conceivable that Graves' disease may constitute an additional risk factor when managing thyroid cancer patients lowering the threshold for surgical intervention.

Color flow Doppler sonography has proven a useful tool in the differential diagnosis of toxic multinodular goiter. Boi et al. have indicated that hyperthyroid patients with multinodular goiter can be subdivided into two distinct groups using color flow Doppler patterns: 1) Nodules with normal vascularization surrounded by hypervascularized hypoechoic thyroid tissue showing a similar picture as in Graves' patients. Notably, in 44% of these patients TSH receptor antibodies were elevated; and 2) heterogenous hypervascularized nodules embedded into normoechoicnormovascular thyroid parenchyma. None of these patients were tested positive for TSH receptor antibodies [35]. The first group constitutes a group of patients, who probably developed Graves' disease in a non-toxic multinodular goiter. Our patient on the other hand showed features of both groups. His prominent nodule was heterogeneous and clearly more vascularized compared to the surrounding thyroid parenchyma matching the ultrasound criteria of group 2). However, his TSH receptor antibody titers were also elevated, indicating that both thyroid autonomy and Graves' disease are concurrent.

Finally, hyperthyroid patients have a disproportionate increase in T3 compared to T4 levels [36]. Laurberg et al. have found that this probably results from a relative increase in type 1 iodothyronine deiodinase activity in hyperthyroid patients compared to healthy subjects, where type 2 iodothyronine deiodinase accounts for the majority of T3 production [37,38]. Our patient with Marine-Lenhart syndrome also presented with an increased T3 to T4 ratio of 1.9%. This matches what Laurberg et al. have found in their collective of multinodular toxic goiter. Their patients with thyroid autonomy had a lower T3/T4 ratio compared to those with Graves' disease (2.0 versus 2.7%) [38], suggesting that in our patient the autonomous adenoma was the more prominent component of disease, which is also supported by the relatively low levels of circulating TSH-RAb and thyroid uptake in the region outside of the adenoma.

Conclusion

Taken together, neither the finding of an autonomously functioning thyroid nodule nor the presence of Graves' disease can rule out a papillary thyroid carcinoma. Although, there is still some debate whether Graves' disease increases the risk for thyroid cancer, nodules embedded in a Graves' goiter should be carefully evaluated for malignant transformation especially when patients are young.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Series Editor of this journal.

Abbreviations

FT4: Free thyroxine; TSH: Thyrotropin or thyroid-stimulating hormone; TT4: Total thyroxine; TT3: Total triiodothyronine; TgAb: Thyroglobulin antibody; TPO: Thyroperoxidase antibody; TSH-RAb: Thyroid stimulating hormone receptor antibody; TBG: Thyroxine-binding globulin; Tq: Thyroglobulin; ND: Not determined.

Competing interest

The authors declare that no financial conflict of interest exists.

Authors' contributions

T.S. compiled data and wrote the manuscript, E.W.K. and M.B.E. researched data and contributed to discussion, C.P. performed thyroid surgery, A.R.C. performed the histologic and molecular analyses, M.K. edited the manuscript and contributed to discussion, A.G. identified the case and wrote the manuscript. All authors read and approved the final manuscript.

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Received: 9 November 2012 Accepted: 23 April 2013 Published: 8 May 2013

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doi:10.1186/1472-6823-13-16

Cite this article as: Scherer *et al.*: A Case of simultaneous occurrence of Marine – Lenhart syndrome and a papillary thyroid microcarcinoma. *BMC Endocrine Disorders* 2013 **13**:16.

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