

Marine-Lenhart syndrome with papillary thyroid carcinoma

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Graves' disease with accompanying functioning nodules is known as Marine-Lenhart syndrome. Autonomously functioning thyroid nodules (AFTNs) also within Graves' thyroid tissue are almost always benign in nature. A 45-year-old man developed hyperthyroidism due to the coexistence of Graves' disease and AFTN. Total thyroidectomy was performed. The hyperfunctioning nodule with centrally hypoactive foci detected by technetium-99m thyroid scanning was histologically diagnosed as papillary thyroid carcinoma that was 2.5 cm in diameter. We report the presence of papillary thyroid carcinoma within AFTN in patients with Marine-Lenhart syndrome, which has not been reported so far.

Key words: Autonomously functioning thyroid nodule, Graves' disease, hyperthyroidism, Marine-Lenhart syndrome, papillary microcarcinoma, papillary thyroid carcinoma, thyroid scintigraphy, toxic nodular goitre

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INTRODUCTION

The coexistence of autonomously functioning thyroid nodules (AFTNs) and Graves' disease has been termed "Marine-Lenhart syndrome".^[1] Different mechanisms are implicated in the pathogenesis of Graves' disease and in AFTN. Graves' disease is caused by the activation of thyrotropin receptor by antithyrotropin receptor antibody; AFTN is caused by autonomously hyperfunctioning nodules. The presence of AFTN within a Graves' thyroid is rare, occurring in about 3% of cases.^[1] It is commonly believed that the diagnosis of AFTN can almost always rule out malignancy in the nodule.^[2] Less than 1% of AFTN harbor malignancies.^[3] Here, we present a case of Marine-Lenhart syndrome with papillary thyroid carcinoma, which is a rare and unusual coexistence.

CASE REPORT

A 45-year-old man was admitted to the Department of Endocrinology, University Hospital of Ondokuz Mayıs University, Samsun, Turkey in 2011, with a 3 months' history of palpitation and right exophthalmos. His medical history was negative for neck or head irradiation. There was no family history of thyroid disease. On physical examination,

a solitary nodule (3 cm in diameter) in the left thyroid lobe was palpated. A mild exophthalmos of the right eye was observed. He had no evidence of Graves' dermopathy. Thyroid function tests showed high levels of free T4 [1.8 ng/dl (normal 0.9-1.7)] and T3 [6.4 pg/ml (normal 2.0-4.4)] with a suppressed thyroid-stimulating hormone (TSH) level [0.005 mIU/mL (normal 0.27-4.2)].

On thyroid ultrasonography, the right lobe was 15 × 25 × 40 mm and the left lobe was 25 × 25 × 55 mm in diameter. In the left lobe, a solid nodule, which was 3 cm in diameter, with necrotic areas was noted [Figure 1]. On technetium-99m thyroid scanning, a diffusely homogenous uptake throughout the gland was noted. A further focal uptake with centrally hypoactive foci corresponding to the ultrasonographically detected nodule was noted in the left lobe [Figure 2]. The degree of exophthalmoses measured with the Hertel exophthalmometer were 17 mm in the left and 21 mm in the right eyes. The antithyroglobulin and antiperoxidase antibodies were below detection levels in the patient. But TSH receptor antibodies were positive (2.36 U/L, normal <1.0). Based on these findings, a diagnosis of Marine-Lenhart Syndrome, which is Graves' disease concurrent with AFTN, was made.

Since the nodule was hyperactive, fine-needle aspiration biopsy (FNAB) was not considered to be of use. The

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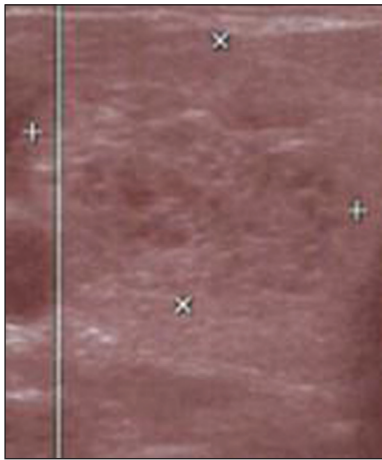


Figure 1: Thyroid ultrasound showing a 3 cm diameter nodule with necrotic areas (crosses denote the contours of the thyroid nodule)

patient was treated with methimazole for several weeks. After establishing euthyroidism, total thyroidectomy was performed. Grossly, the right lobe measured $4 \times 2.5 \times 1.5$ cm and the left lobe measured $5.5 \times 2.5 \times 2.5$ cm. Macroscopic examination of the thyroid gland revealed nodules with multiple foci, the largest of which was 0.6 cm in the right lobe, and a 2.5 cm solitary nodule in the left lobe. The pathologic diagnosis of the right lobe was papillary microcarcinoma with the follicular variant. Two of the foci measured 1 mm and 2 mm in diameter. The nodule on the left lobe was a follicular variant of papillary carcinoma, measuring 2.5 cm in diameter. Immunohistochemically, the tumor was positive for cytokeratin 19 and galectin 3. Capsule invasion, lymphovascular invasion, and extrathyroidal extension were not seen.

Subsequently, the patient underwent 100 mCi ^{131}I radioactive ablation therapy. Posttreatment scanning showed no significant ^{131}I uptake in the thyroid bed or elsewhere in his body. Thyroglobulin concentration was <0.2 ng/ml. Suppressive thyroid supplementation was started.

DISCUSSION

We report a patient with Marine-Lenhart Syndrome concurrent with thyroid papillary carcinoma, which is a very unusual presentation of this syndrome.

The risk of thyroid malignancy in patients with concomitant autonomously functioning nodules continues to be underestimated in clinical practice due to its low occurrence and the misconception that the coexistence of a "hot" nodule and thyroid carcinoma are very rare.^[4] The likelihood of a carcinoma within a hot nodule is below 1%.^[5] Therefore, it is commonly believed that the diagnosis of AFTN can almost always rule out malignancy in the nodule.^[2] According to

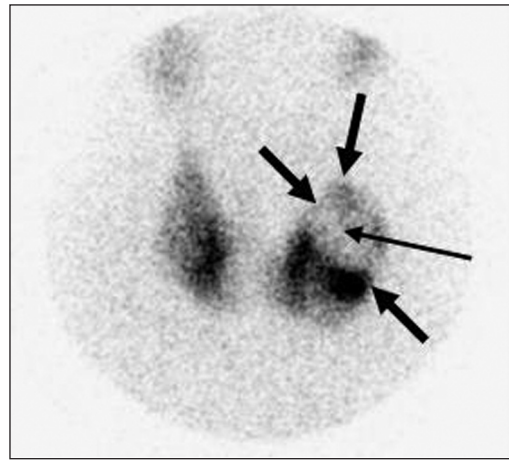


Figure 2: Tc-99m pertechnetate showing a diffusely homogenous uptake in both lobes of the gland and a hyperfunctioning nodule (thick arrows) with centrally hypoactive foci (thin arrow) in the left lobe

guidelines, nodules that are hot on scintigraphy should be excluded from FNAB.^[6]

The type of scintigraphy employed in this type of imaging is important. Thyroid scan can be performed with iodine-123, iodine-131, or technetium-99-labeled pertechnetate. Iodine isotopes, which are both trapped and bound organically in the thyroid, are preferred, since 3%-8% of nodules that appear functioning on pertechnetate scanning may appear nonfunctioning on radioiodine (RAI) scanning, some of which may be malignant.^[7]

The association of hyperfunctioning thyroid node and carcinoma has been classified as follows:^[8]

1. The coexistence of carcinoma and focally hyperfunctioning tissue in the same gland but at different locations (a relatively common finding);
2. The presence of a large tumor mass that can compete with normal tissue for tracer uptake, despite being hormonogenetically ineffective by itself;
3. Carcinoma located in a hyperfunctioning adenoma;
4. Real hyperfunctioning carcinoma (extremely rare). The last two conditions have a potential for erroneous diagnosis if hot or warm nodes are always considered benign as in 4, or, if focal hypofunctions in a plummerian node are always regarded as degenerative colliquative events as in 3. This case falls into the third of these categories. Upon thyroid scintigraphy, a hypofunctioning area within the hyperactive node was initially interpreted as necrotic, which was also noted by ultrasonography.

Some patients with toxic multinodular goitre may be positive for thyroid autoantibodies. Differential diagnosis between these patients and Marine-Lenhart Syndrome is based on the appearance of thyroid scan. In patients with

toxic multinodular goiter, increased uptake is seen on the sonographically defined areas of nodules, and the rest of the gland is suppressed.

In Marine-Lenhart syndrome, there is a diffuse and increased uptake in the gland in general, with foci of further enhanced uptakes by the nodules.^[9] Most reports showed hyperactivity in the extranodular parenchyma and relative hypoactivity in the nodule at initial scintigraphy of Marine-Lenhart Syndrome.^[10] It has been suggested that the tissue within the nodule becomes suppressed by the overactivity of the unaffected gland and therefore does not take up tracer or RAI.^[10] However, increased homogenous uptake was also noted in a report in the extranodular tissue with intense focal uptake in the nodules.^[9] Moreover, there is also a report showing similar activity between nodules and extranodular tissues.^[11] In this patient, a diffusely homogenous uptake throughout the gland and a further focal uptake with centrally hypoactive foci corresponding to the ultrasonographically detected nodule were noted.

The prevalence of concomitant thyroid carcinoma with Graves' disease has been reported to range from 1.1 to 7.1%.^[5] The majority of these carcinomas are arising from cold nodules. Papillary thyroid microcarcinoma is the most common histologic subtype.^[12]

It appears that RAI treatment has a risk of progressing to Graves' ophthalmopathy.^[13] In addition, it has been suggested that functioning nodules in patients with Marine-Lenhart syndrome are more radio resistant compared to Graves' disease without nodules.^[1] Hence, RAI treatment was ruled-out in our patient based on these reports. The patient underwent thyroidectomy for hyperthyroidism and a hyperfunctioning nodule.

We found only one case in the literature reporting micropapillary thyroid carcinoma detected in the hyperfunctioning nodule in a patient with Graves' disease.^[14] The reported carcinomas within the hyperfunctioning thyroid nodules are more often papillary microcarcinomas.^[4] Malignant tumors of more than 1 cm diameter are very rare.^[15]

To our knowledge, this is the first case describing the coexistence of thyroid cancer of more than 1 cm in diameter in patients with Marine-Lenhart Syndrome. Even if a hyperfunctioning thyroid carcinoma is an extremely rare malignancy, careful management, especially in cases with a cold area within a hot nodule, is recommended.

AUTHOR'S CONTRIBUTIONS

HA contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

RÇ contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

ZAY contributed in the English writing, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

MK contributed in the pathological evaluation of the specimen of the patient, approval of the final version of the manuscript, and agreed for all aspects of the work.

FCT contributed in the interpretation of imagine of the thyroid scanning and ultrasonography, approval of the final version of the manuscript, and agreed for all aspects of the work.

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