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Marine-Lenhart syndrome: A rare cause of thyrotoxicosis

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Introduction

Marine-Lenhart syndrome (MLS) is a rare thyroid disorder characterized by the coexistence of Graves' disease with autonomously functioning thyroid nodules. First described by Marine and Lenhart in 1911, the syndrome represents a unique subset of hyperthyroidism, wherein patients exhibit clinical features of Graves' disease (GD) alongside the presence of one or more thyroid nodules that function independently of thyroid-stimulating hormone (TSH) regulation.[1] This combination can complicate clinical presentation and management, as it merges the autoimmune hyperthyroidism seen in GD with the nodule-driven hormone production typical of toxic nodular goiter.

The diagnosis of MLS can be challenging due to its overlap with other thyroid pathologies, such as Plummer's disease (toxic multinodular goiter).[2] Accurate differentiation is critical as the treatment approach may vary depending on the underlying pathology. Advances in imaging techniques, such as thyroid scintigraphy and ultrasonography, alongside laboratory assessments of thyroid function, have improved our ability to identify this syndrome, yet it remains underreported in clinical practice.

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In this case report, we present a female in her 30s who presented with thyrotoxic symptoms and was subsequently diagnosed with MLS. This report highlights the diagnostic challenges, clinical features, and therapeutic considerations of this uncommon thyroid disorder.

Case Report

A 32-year-old female presented to the outpatient department with complaints of weight loss, palpitations, heat intolerance, and nervousness for the past two months. She also reported experiencing increased sweating and fatigue. There was no significant family history of thyroid disorders, and she had not been on any medications that could affect thyroid function.

On examination, the patient had a slightly enlarged thyroid gland with no palpable nodules. Her pulse rate was 110 beats per minute, regular, and her blood pressure was 124/80 mmHg. The patient exhibited a fine tremor in her hands, and her skin was warm and moist. No exophthalmos or pretibial myxedema was observed. Laboratory tests revealed elevated serum thyroxine (T4) of 14.2 µg/dL [normal range (N): 4.5-11.2 µg/dL], elevated serum tri-iodothyronine (T3) of 220 ng/dL (N: 80-180 ng/dL), elevated free thyroxine of 2.8 ng/dL (N: 0.8-1.8 ng/dL), elevated free tri-iodothyronine (FT3) of 8.0 pg/mL (N: 2.3-4.2 pg/mL) and suppressed thyroid stimulating hormone (TSH) of less than 0.01 µIU/mL (N: 0.5-4.5 µIU/mL), all measured by chemiluminescence (CLIA). A technetium-99m thyroid scan showed increased uptake in a single "hot" nodule located in the right lobe of the thyroid gland, with a relatively suppressed uptake in the remaining gland tissue. Ultrasonography (USG) (Image A) confirmed the presence of a hypoechoic nodule in the right lobe, measuring 2.5 x 2.0 cm with increased blood flow on the doppler study (Image B) Fine needle aspiration cytology (FNAC) of the right thyroid nodule revealed clusters of benign thyroid follicular in the background of occasional cyst macrophages, scant colloid, and red blood cells, categorized as Bethesda category 2, indicating a benign lesion. The patient's TSH receptor antibody (TRAb) levels were significantly elevated, 10.74 IU/L (N<1.54 IU/L), consistent with Graves' disease. The clinical, biochemical, and imaging findings led to the diagnosis of MLS, characterized by GD with a coexisting autonomous hot nodule.

The patient was initiated on carbimazole 30 mg daily in three divided doses. This approach aimed to control the overall hyperthyroid state induced by both the diffuse thyroid activity and the autonomous nodule. After three months of treatment, her thyroid function tests normalized, allowing for a reduction in the carbimazole dose to 15 mg/day. The patient's youngest child was

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two years of age. After a shared decision-making process with the patient, it was agreed to continue the anti-thyroid drug (ATD) for at least a year, taking into account her personal circumstances. Given that radioiodine ablation therapy (RAIA) requires isolation for a few days, it was considered prudent to defer RAIA until the patient's child is slightly older and the patient's clinical condition remains stable.

Discussion

Marine-Lenhart syndrome (MLS) is a rare clinical condition characterized by the coexistence of Graves' disease and autonomous thyroid nodules. The diagnostic criteria for this condition are not well established. David Charkes coined the term in 1972, identifying key characteristics, such as the following:[3]

1. **TSH Stimulation**: When stimulated by TSH, these nodules show increased radioiodine uptake, unlike the hyperfunctioning nodules of Plummer's disease, with a response quantified as 1.7 times greater or more,

2. **Scintigraphy Appearance**: On scintigraphy, the nodules appear "cool," indicating reduced radioiodine accumulation compared to the surrounding thyroid tissue, which differs from what is observed in Plummer's disease,

3. **Radioiodine Resistance**: These nodules are more resistant to standard radioiodine treatment and thus require higher doses of iodine-131 (I-131)than patients with typical GD,

4. **Post-Treatment Uptake**: After successful I-131 treatment, the nodules show a relative increase in radioiodine uptake, a response not seen in Plummer's disease,

5. **Pathology**: The pathology of these nodules typically reveals adenomas.

Charkes estimated the prevalence at 2.7%,[3] though other studies suggest a lower prevalence of 0.8%.[4] Although the cases initially described by Marine, Lenhart, and Charkes reported "cool" nodules on scintigraphy, there have since been reports of Graves' disease coexisting with "hot" nodules.[5, 6] This has led to the recognition of a variant of MLS, where functioning "hot" nodules are present alongside GD. Cases of MLS with papillary thyroid carcinoma (PTC) have also been reported.[7]

To settle these discrepancies, Neuman et al have proposed the following for the diagnosis of MLS. (1) thyroid function tests consistent with hyperthyroidism inclusive of serological testing for GD (TRAb); (2) increased radioiodine uptake and the presence of "cool" or "hot" nodules; thyroid nodularity should be supported by ultrasonography; (3) thyroid nodule biopsy revealing a hyperplastic lesion or follicular adenoma, although, in the latter case, diagnostic surgery may be required to rule out a follicular carcinoma.[2]

One important consideration in the management of MLS is the potential cancer risk associated with thyroid nodules. While most autonomous thyroid nodules are benign, the presence of a nodule within the context of GD, as seen in MLS, raises additional concerns. Although the overall risk of malignancy in autonomous nodules is low, studies suggest a slightly increased risk in patients with MLS compared to those with GD alone.[7-9] Therefore, careful evaluation and monitoring of the nodule are essential. Fine needle aspiration cytology (FNAC) is a critical tool in assessing the nature of the nodule, as was done in this case, where the nodule was found to be a benign colloid goiter (Bethesda category 2).

The management of MLS differs from that of isolated GD or a solitary toxic nodule. In GD, treatment typically focuses on controlling diffuse thyroid hyperactivity, often with ATDs, RAIA or surgery. The presence of a hyperfunctioning nodule in MLS complicates this approach. While ATDs can effectively manage the hyperthyroid state, they do not address the autonomy of the nodule, which may continue to produce thyroid hormones independently. This necessitates a more tailored approach, often involving RAIA or surgery to ablate or remove the nodule, especially if it grows or remains active despite medical therapy.

The remission rate in MLS is generally lower than in GD alone. GD has a variable remission rate, with studies suggesting that about 20-30% of patients achieve long-term remission after ATDs. However, the presence of an autonomously functioning nodule in MLS often reduces the likelihood of achieving remission without definitive treatment, such as RAIA or surgery.

Conclusion

In summary, Marine-Lenhart syndrome requires a nuanced and individualized approach to management, taking into account the potential cancer risk of the nodule, the reduced remission rate compared to Graves' disease, and the need for a combination of therapies. Close monitoring,

patient involvement in decision-making, and a tailored treatment strategy are essential for optimizing outcomes in this rare and complex condition.

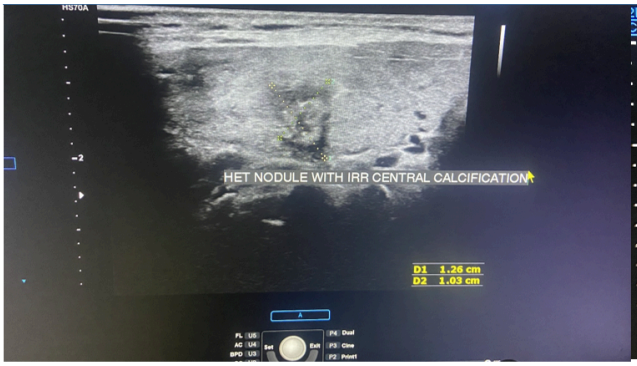


Image- A

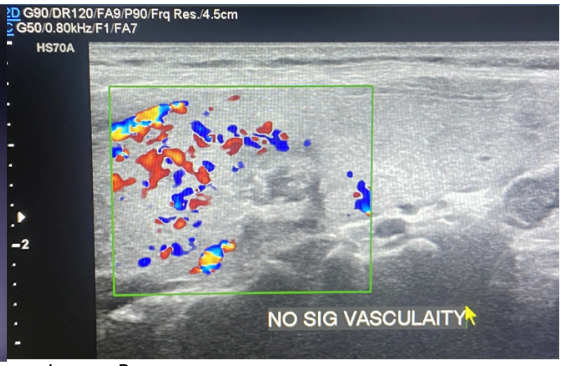
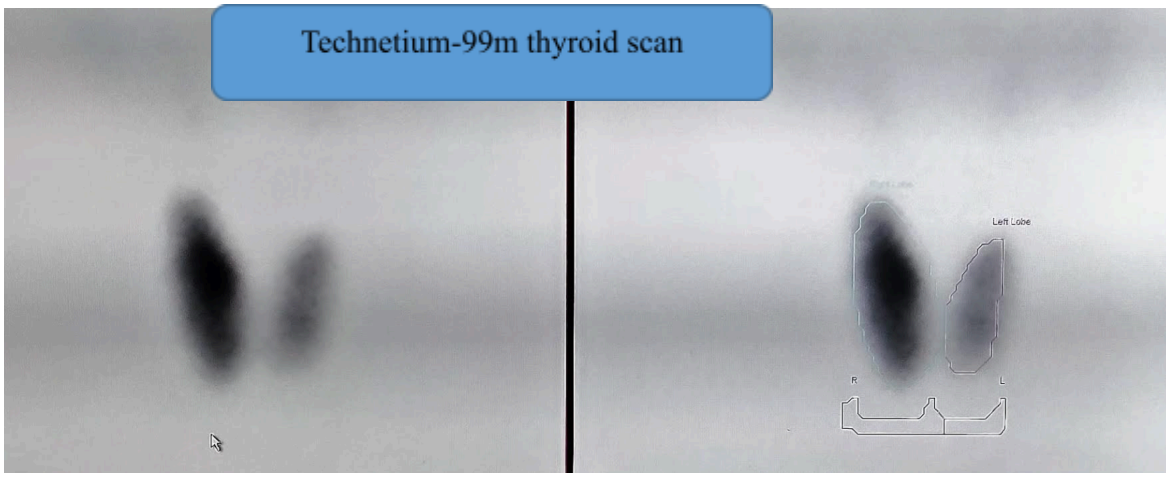


Image- B

USG neck of the patient showing small ill defined heterogeneous nodule with central irregular calcification in right lobe of thyroid (Image- A) with no significant vascularity on doppler study(Image- B).



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