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Case Report

Mild Thyrotoxicosis due to Seronegative Graves' Disease or Disseminated Thyroid Autonomy

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ABSTRACT

Background/Objective: Disseminated thyroid autonomy (DTA) and seronegative Graves' disease are rare causes of hyperthyroidism with similar clinical presentations. This case report highlights the diagnostic challenges between these entities.
Case Presentation: A 35-year-old male presented with palpitations, diaphoresis, and a small goiter. His TSH was 0.249 mIU/L (reference: 0.45–4.5 mIU/L) and free T4 was 3.0 ng/dL (reference: 0.88–1.77 ng/dL). Thyroid peroxidase antibodies, TRAb, and TSI were repeatedly negative. Ultrasound showed a diffusely enlarged thyroid, and radioactive iodine uptake was 35% (reference: 10% to 35%) with thyroid scintigraphy revealing diffusely increased uptake, indicating a hyperfunctioning thyroid without nodules. Treatment with Methimazole 5 mg daily resolved symptoms within 6 months.
Discussion: Thyroid biopsy can help distinguish DTA from seronegative Graves disease. DTA is marked by nodular hyperplasia without lymphocytic infiltration, indicating a non-autoimmune nature, while seronegative Graves' disease exhibits diffuse follicular hyperplasia with lymphocytic infiltration, just as typical Graves' disease despite undetectable autoatibodies. The possibility of false-negative TRAb results complicates diagnosis, with up to 22% of patients initially diagnosed with DTA later testing TRAb-positive upon retesting. Some cases of DTA may involve TSH receptor gene mutations.
Conclusion: This case highlights the complexity of distinguishing DTA, seronegative Graves' disease and typical Graves' disease with initial false negative testing. A systematic approach with repeat testing and, when feasible, biopsy, is critical to distinguish these entities. Further studies with histologic analysis are needed to clarify outcomes and develop tailored managements, as these conditions have different remission rates and are driven by different mechanisms.

Introduction

Disseminated thyroid autonomy (DTA) is one of the 3 described forms of thyroid autonomy, along with unifocal and multifocal autonomy, and is seldom mentioned in clinical guidelines. Rarely referenced in nuclear radiology literature, DTA poses a unique diagnostic challenge due to its clinical and imaging similarities with classical Graves' disease. Both conditions present with symptoms of hyperthyroidism, elevated T4 and T3 levels, suppressed TSH, goiter, and a high radioactive iodine uptake, with a diffusely increased uptake pattern on Tc-99m thyroid scintigraphy, complicating their differentiation. The presence of a seronegative variant of Graves' disease, in which autoimmunity is

Abbreviations: AUC, area under the curve; β-HCG, beta-human chorionic gonadotropin; DTA, disseminated thyroid autonomy; FSH, follicle-stimulating hormone; FT4, free thyroxine; LH, luteinizing hormone; RAIU, radioactive iodine uptake; TBII, thyrotropin-binding inhibitory immunoglobulin; TPO Ab, thyroid peroxidase antibodies; TRAb, thyroid-stimulating hormone receptor antibodies; TSH, thyroid-stimulating hormone; TSI, thyroid stimulating immunoglobulin; TT3, total triiodothyronine; US, ultrasound.

STATEMENT OF PATIENT CONSENT: Signed informed consent was obtained directly from the patient.

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presumed but not confirmed by current assays, further adds to the complexity. Graves' disease itself is an autoimmune disorder driven by TSH receptor stimulation, resulting in hyperthyroidism. Although seronegative Graves' disease lacks detectable antibodies, it is still regarded as autoimmune due to its histological resemblance to Graves' disease, a distinction that may be limited by the sensitivity of current testing. Conversely, DTA is considered nonautoimmune, sharing similar hormone profiles and imaging features with Graves but differing in its distinct histological findings and lack of autoantibodies.[1,2] This case report underscores the diagnostic challenges and clinical overlap between these conditions.

Case Presentation

A 35-year-old male presented to our clinic with daily episodes of brief palpitations lasting a few minutes and frequent episodes of diaphoresis over the past 2 years. His medical history included prediabetes and essential hypertension. He denied any family history of autoimmune diseases or hyperthyroidism. Physical examination revealed a blood pressure of 132/89 mmHg, a heart rate of 105 beats per minute, a weight of 183 lbs, and a BMI of 25.6. His face appeared flushed, and his skin was warm and moist. A small, nontender goiter was noted, without palpable nodules, as well as a mild tremor on arm extension. His fingernails were thin and brittle. There were no abnormal lymph nodes detected in the neck, and ocular examination showed no signs of proptosis, lid lag, or chemosis.

An electrocardiogram revealed sinus tachycardia at a rate of 112 beats per minute with no other abnormalities. Initial laboratory tests 2 years prior, conducted at an outside facility for initial evaluation of his goiter indicated TSH of 0.437 mIU/L (normal range: 0.45-4.5 mIU/L) and a FT4 level at 1.52 ng/dL (19.54 pmol/L) (normal range: 0.88-1.77 ng/dL; 11.6-29.6 pmol/L).

Thyroid peroxidase and TSH receptor antibodies (TRAb) tests at that time were negative.

As the patient was asymptomatic, no treatment was initiated, and the decision was made to monitor his condition with repeat blood work. One year later, follow-up testing showed a further decrease in TSH to 0.219 mIU/L and an increase in FT4 to 2.2 ng/dL. However, the patient was lost to follow-up, and no intervention was provided. Finally, 2 years later, upon presenting to our clinic with the new symptoms mentioned above, we conducted our own laboratory tests, which showed FT4 of 3.0 and TSH of 0.249 (refer to Table for a summary of results). Repeat tests for TRAb using a second-generation assay, thyroid stimulating immunoglobulins, and thyroid peroxidase antibodies were all negative. Thyroid ultrasound demonstrated a diffusely enlarged gland, with a right lobe measuring 5.9 × 2.3 × 1.9 cm, left lobe measuring 6.1 × 2.8 × 2 cm, and an isthmus thickness of 0.24 cm. The gland appeared homogeneous in texture, with normal vascularity and no discrete nodules (Fig. 1). Radioactive iodine uptake testing with an orally administered 11 μCi iodine-131 capsule revealed an uptake of 35% at 24 h, at the upper limit of normal. A subsequent thyroid scintigraphy using 10.4 mCi of technetium-99m pertechnetate showed a normal thyroid configuration with uniform radionuclide uptake (Fig. 2). Additional biochemical tests were conducted to measure levels of hormones that share an alpha subunit similar to TSH, including luteinizing hormone (LH), follicle-stimulating hormone, and beta-human chorionic gonadotropin. These levels were within normal limits.

After carefully excluding other possibilities, a provisional diagnosis of either DTA or seronegative Graves' disease was made. A thyroid biopsy was not performed, as per the patient's preference. Treatment options, including thionamides, radioactive iodine ablation, and surgical resection, along with their potential complications, were discussed in detail. A shared decision was made to start Methimazole, with an empiric initial dose of 5 mg daily, based on his symptoms, TSH, and FT4 levels at presentation.

Highlights

- DTA and seronegative Graves overlap in presentation, complicating differentiation
- Biopsy is crucial for distinguishing DTA from seronegative Graves
- DTA may involve TSHR mutations (eg, L512Q, E575K) suggesting a genetic component
- Seronegative Graves may stem from local antibody production undetectable in serum
- Remission is less likely in DTA, often requiring lifelong treatment or ablation

Clinical Relevance

This case highlights the importance of a systematic approach and the necessity of repeat testing in diagnosing disseminated thyroid autonomy and seronegative Graves' disease, 2 diagnoses of exclusion that require careful confirmation to avoid false negatives and to guide effective long-term management, given their lower remission rates compared to typical Graves' disease.

Outcome and Follow-Up

At a 6-month follow-up, both his TSH and FT4 had normalized. His blood pressure had greatly improved, allowing discontinuation of his antihypertensive medications. Additionally, his palpitations, sinus tachycardia, and episodes of diaphoresis had resolved.

Discussion

The patient's symptoms, biochemical profile, and imaging findings are consistent with hyperthyroidism; however, the absence of detectable TSH receptor antibodies complicates the diagnosis. Given the diffusely increased uptake pattern on Tc-99m scintigraphy, DTA remains a strong possibility, particularly in the absence of autoantibodies typically seen in Graves' disease. Nevertheless, the gradual progression from subclinical to overt hyperthyroidism, along with the homogeneous thyroid ultrasound findings, aligns with patterns observed in seronegative Graves' disease as well. Without a biopsy to confirm histological differences, this case exemplifies the difficulty in distinguishing DTA from seronegative Graves' disease, as both conditions share overlapping clinical and imaging characteristics.

Graves' disease is characterized by autoimmune stimulation of the TSHR, leading to hyperthyroidism. The diagnostic criteria currently accepted for Graves' disease, as outlined by the American Thyroid Association, include positive TSHR antibodies, suppressed TSH levels accompanied by elevated FT4 or FT3, and, when further confirmation is required, a thyroid ultrasound demonstrating increased vascularity.[3] Histologically, Graves' disease shows diffuse follicular hyperplasia along with prominent lymphocytic infiltration and fibrous connective tissue, characterizing its autoimmune nature. A seronegative variant of Graves' disease also exists, in

Table
Chronological Summary of Testing and Management

Test	Initial	Month 12	Month 26	Month 36	Month 42	Normal range
FT4	1.52 ng/dL (19.5 pmol/L)	2.2 ng/dL (28.34 pmol/L)	1.59 ng/dL (20.4 pmol/L)	3.0 ng/dL (38.6 pmol/L)	1.7 ng/dL (21.9 pmol/L)	0.88-1.77 ng/dL (11.6-29.6 pmol/L)
TT3		116 ng/dL				71-180 ng/dL (1.09-2.76 nmol/L)
TSH	0.437 mUI/mL	0.210 mUI/mL	0.363 mUI/mL	0.243 mUI/mL	0.49 mUI/mL	0.45-4.5 mUI/mL
TPO Ab	9 IU/mL		12 IU/mL	< 8 IU/mL		0-34 IU/mL
TRAb	< 1.10 IU/L	< 1.10 IU/L		< 1.10 IU/L		< 1.75 IU/L
TSI	< 0.10 IU/L					0.00-0.55 IU/L
Thyroid US			Enlarged		Enlarged	
RAIU				35% at 24 h		10-35% at 24 h
Thyroid Scintigraphy				Diffuse uptake		
LH				4.6 mIU/mL		1.24-8.62 mIU/mL
FSH				3.0 mIU/ml		1.27-19.26 mIU/ml
β-HCG (Qualitative)				Negative		Qualitative cutoff value is 5 mIU/mL
Treatment				Methimazole 5 mg daily	Methimazole 5 mg daily	

Abbreviations: β-HCG = beta-human chorionic gonadotropin; FSH = follicle-stimulating hormone; LH = luteinizing hormone; RAIU = radioactive iodine uptake; TRAb = TSH receptor antibodies; TSI = thyroid stimulating immunoglobins.

which TRAb or TSI antibodies are undetectable despite similar clinical and histologic findings. This histologic similarity suggests an underlying autoimmune component that may evade our current diagnostic tools. On the other hand, DTA, which is rarely discussed in guidelines, can also mimic Graves' disease due to similar hormone profile and imaging features. However, DTA is considered nonautoimmune in nature, due to its distinct histologic finding of nodular hyperplasia without the lymphocytic infiltration characteristic of Graves' disease and its seronegative variant.[4]

Thyroid autonomy is an umbrella term that includes unifocal thyroid autonomy (autonomous or toxic adenoma), multifocal thyroid autonomy (multiple autonomous regions within a multinodular, often euthyroid goiter), and DTA, which is marked by increased uptake throughout the entire gland. All forms of thyroid autonomy involve independent hormone production by thyroid tissue functioning outside the hypothalamic-pituitary-thyroid regulatory axis, each distinguishable through scintigraphy imaging.[5]

It is important to clarify that "disseminated" does not imply hormone production outside the thyroid gland but rather indicates increased activity across the entire gland, unlike the focal and multifocal forms, where hyperactivity is limited to nodular areas.

DTA, although a prominent cause of hyperthyroidism in iodine-deficient regions[6], is seldom mentioned in the literature, likely because of the need for histologic testing to distinguish it. As a result, DTA is often grouped with seronegative Graves' disease in studies. One particular study involving 258 patients with newly diagnosed hyperthyroidism and biochemical profiles indicative of Graves' disease found that 5.4% were seronegative when tested with a second-generation thyrotropin-binding inhibitory immunoglobulin (TBII) assay. However, no effort was made to distinguish between DTA and seronegative Graves' disease in these cases. Interestingly, seronegative patients exhibited milder biochemical thyrotoxicosis than seropositive patients, with a direct correlation between TBII levels and both fT3 and fT4 indices. Furthermore, seronegative patients had distinctive clinical characteristics, including the absence of Graves orbitopathy and pretibial myxedema, along with smaller goiters, lower thyroid hormone levels, lower radioiodine uptake, and smaller thyroid volumes compared to seropositive patients. Further stratification through histologic analysis would have been useful to differentiate DTA from seronegative Graves' disease in this subset.[7]

A study conducted in Germany in 2000 evaluated 370 patients treated with Iodine 131 for hyperthyroidism, initially presenting with characteristics of Graves' disease. Of these, 7.6% tested negative for TSHR antibodies, suggesting a possible diagnosis of DTA. But later, 22% of those initially diagnosed with DTA were found to be TRAb-positive upon retesting with a second-generation assay. This finding highlights the possibility of initial false-negative results and underscores the necessity for confirmatory repeat testing to ensure accurate diagnosis.[8] In a 2019 study, ROC curve analysis compared second- and third-generation TRAb ELISAs across various patient groups, finding no significant improvement in diagnostic accuracy with the newer assay. The third-generation assay recorded area under the curve AUC values comparable to the second generation, underscoring the ongoing challenge of accurately differentiating Graves' disease from DTA.[9]

A possible genetic component for DTA has been highlighted by several studies including a longitudinal study at Kuma Hospital in Japan, which followed approximately 25 000 hyperthyroid patients from 2003 to 2012. Among these, 89 patients with diffuse

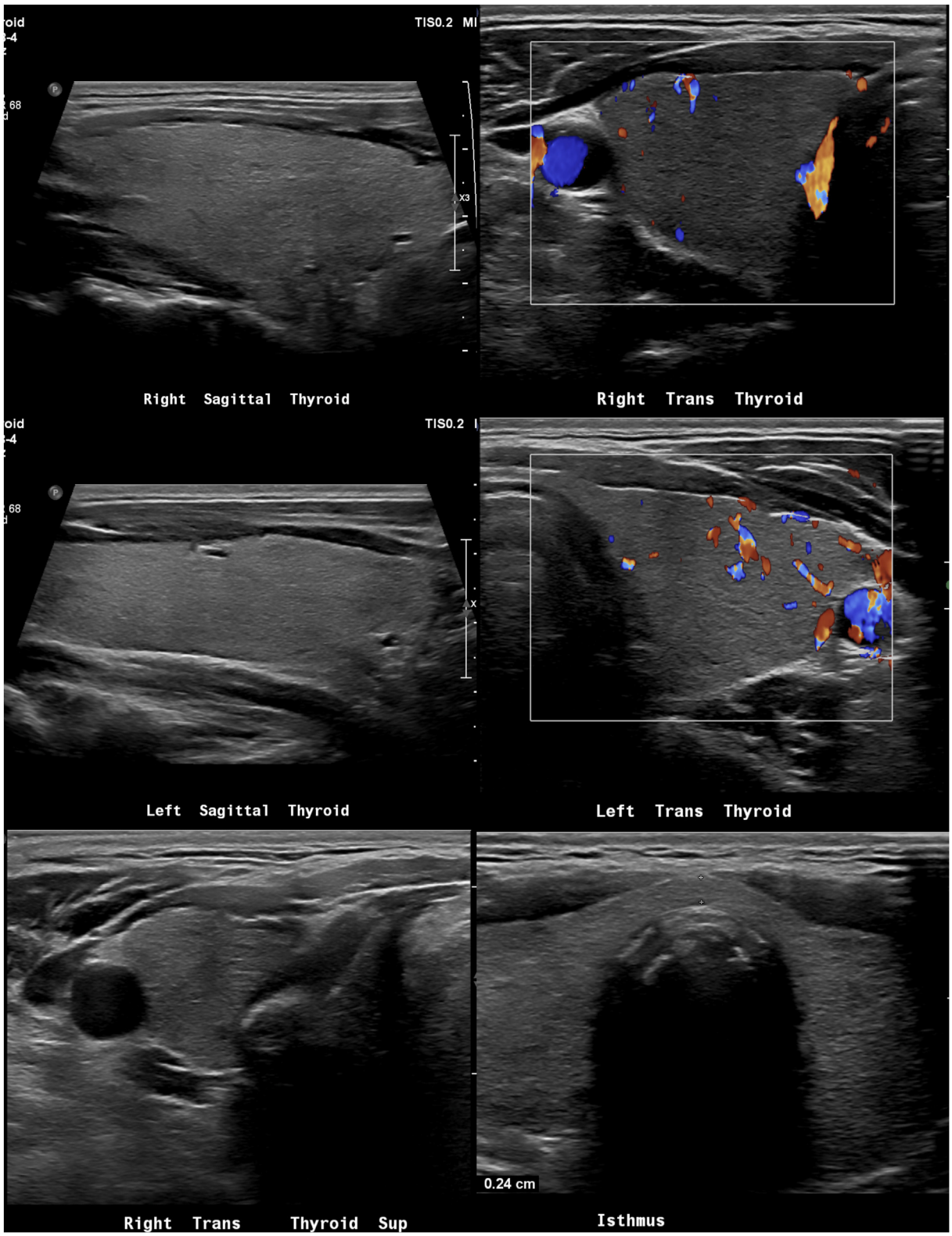

Fig. 1. Ultrasound of the thyroid showing diffusely enlarged thyroid gland, *right* lobe 6.1 × 2.8 × 2 cm, *left* lobe 6.1 × 2.8 × 2 cm, isthmus thickness 0.24 cm, the approximate total volume of 13.5 ml (normal:7 - 10 mL), thyroid appears homogeneous without evidence of discrete nodules or increased vascularity.

goiters consistently lacked measurable TSHR directed antibodies across repeated tests over the years. Notably, 4 of these 89 patients (4.5%) had activating mutations in the TSHR gene, with 3 cases involving constitutively activating mutations (L512Q, E575K, and D617Y). Family screening identified additional carriers of these mutations, suggesting a hereditary component in certain cases of suspected DTA. The study also found that patients with persistently negative TSHR antibody tests often exhibited less severe, but

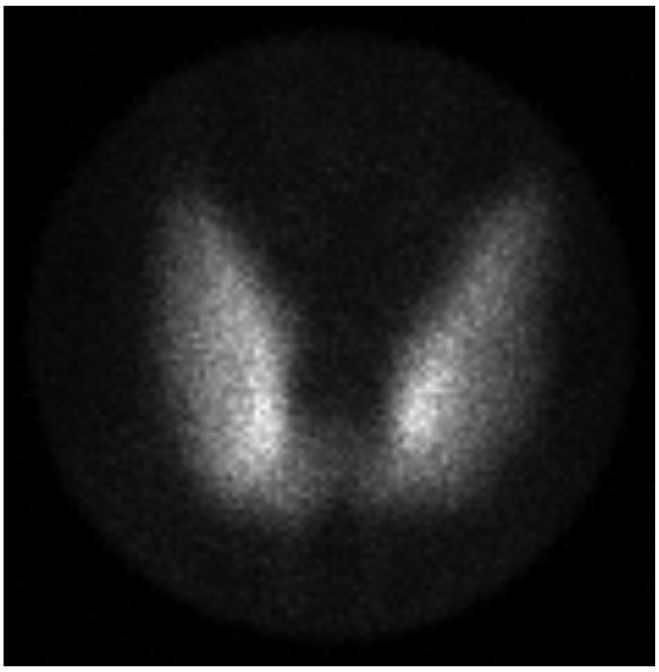

Fig. 2. Thyroid scintigraphy using technetium-99m pertechnetate, demonstrating a normal thyroid configuration with uniform radionuclide uptake. The Radioactive Iodine Uptake done prior to the scintigraphy was 35% 24 h after ingesting 11 uCi of iodine-131 (reference range 10% to 35% at 24 h).

nonremitting hyperthyroid symptoms, necessitating extended medical management or earlier consideration for thyroid ablation compared to those with detectable TSHR antibodies.[10,11]

A question arises as to how seronegative Graves' disease exists given that TSHR-stimulating antibodies are central to its pathophysiology. One possible explanation is that even advanced second and third-generation TBII assays may lack the sensitivity to detect very low levels of these antibodies. Earlier studies using cytochemical bioassays based on enzymatic responses within thyroid tissue demonstrated sensitivities at least ten times higher than modern assays.[12] Another possibility is that TSHR antibody production and circulation may be confined to the thyroid gland and nearby lymph nodes, resulting in levels too low to be detected in the bloodstream. Supporting this theory, a research has found that lymphocytes isolated from the thyroid gland of a patient with autoimmune thyroiditis, despite a lack of detectable serum autoantibodies, were producing multiple antithyroid antibodies.[13] Furthermore, lymphoid follicles within the thyroid can provide the complete environment necessary to initiate and sustain an autoimmune response.[14]

In summary, this case underscores the diagnostic complexity of distinguishing DTA from seronegative Graves' disease in the absence of autoantibodies. Despite a thorough evaluation of clinical presentation, imaging, and biochemical markers, a thyroid biopsy remains crucial for differentiation between these entities. Finally, additional longitudinal studies that include histologic testing to distinguish DTA from Graves' disease and its seronegative variant are needed to better characterize outcome differences and, ultimately, to develop tailored management strategies based on their unique mechanisms.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

We have no acknowledgments to declare.

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