# HYPERFUNCTIONING NODULAR GOITER ASSOCIATED WITH GRAVES' ORBITOPATHY AND PAPILLARY CARCINOMA: A CASE SERIES AND REVIEW OF LITERATURE

Marjeta Kermaj, Dorina Ylli, Violeta Hoxha, Agron Ylli
Department of Endocrinology, U.H.C. "Mother Teresa," Tirana, Albania.

Corespondent E-mail: marjetak17@gmail.com.

**Abstract**

This article presents a case series of three patients diagnosed with hyperfunctioning nodular goiter associated with Graves' orbitopathy, one of whom was also found to have papillary thyroid carcinoma. The rarity of coexisting Graves' orbitopathy, and toxic nodular goiter is discussed, highlighting the emergence of Graves' disease in such cases.

**Introduction:** The coexistence of Graves' orbitopathy and toxic nodular goiter is a rare occurrence, representing the emergence of Graves' disease.While hyperthyroidism is believed to protect against thyroid cancer, recent studies suggest that the incidence of malignancy in toxic nodular goiter is not as low as previously thought.

**Methods:** Detailed clinical, laboratory, and radiological findings of the three cases are provided, with diagnostic confirmation achieved through 99m Tc thyroid scintigraphy, confirming toxic nodular goiter as the cause of hyperthyroidism. Biopsy post-total thyroidectomy revealed papillary thyroid carcinoma in one case. Treatment options, including antithyroid drugs, synthetic glucocorticoids, and surgical interventions, are discussed.

**Results:** All three cases presented with hyperthyroidism and Graves' orbitopathy, with two undergoing total thyroidectomies, uncovering papillary thyroid carcinoma within toxic adenomas. The third patient opted for methimazole treatment. The successful management of Graves' orbitopathy with high-dose pulse glucocorticoids is discussed, along with the challenges of managing toxic nodular goiter and active Graves' orbitopathy concurrently.

**Conclusion:** Toxic nodular goiter accompanied by infiltrative ophthalmopathy represents the emergence of Graves' disease, confirmed by the presence of Antibodies to the thyrotropin receptor. Surgical intervention is considered a crucial therapeutic modality, especially in cases where toxic nodular goiter coexists with Graves' orbitopathy. The article underscores the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in such complex cases.

**Keywords:** Hyperfunctioning nodular goiter, Graves’orbitopathy, papillary thyroid carcinoma, thyrotropin-stimulating hormone receptor antibodies.

# STRUMA NODULARE HIPERFUNKSIONANTE E SHOQËRUAR ME GRAVES'ORBITOPATI DHE KARCINOMË PAPILARE: NJË SERI RASTESH KLINIKE DHE RISHIKIM I LITERATURËS


## Abstrakt

Ky artikull paraqet tre raste të pacientëve të diagnostikuar me strumë nodulare toxike të shoqëruar me orbitopatinë e Graves ku njëri prej tyre kishte karcinomë papilare të tiroides.
**Hyrje:** Bashkëekzistenca e orbitopatisë e Graves dhe struma nodulare toxike është një dukuri e rrallë. Ndërsa hipertiroidizmi besohet se mbron nga kanceri i tiroides, studimet e fundit sugjerojnë se incidenca e tumoreve malinje në strumë nodulare toxike nuk është aq e ulët sa mendohej më parë.
**Metodat:** Përfshijnë gjetjet klinike, laboratorike dhe radiologjike, konfirmuar me shintigrafi të tiroides 99m Tc për strumë nodulare toxike. Diskutohet menaxhimi i suksesshëm i orbitopatisë së Graves dhe sfidat e trajtimit të strumës nodulare toxike dhe orbitopatinë e Graves njëkohësisht.
**Rezultatet:** Të tre rastet u paraqiten me hipertiroidizëm dhe orbitopatinë e Graves, ku dy iu nënshtruan tiroidektomisë totale, ku biopsia post operatore zbuloi karcinomë papilare të tiroides në një rast, brenda adenomes toksike. Pacienti i tretë zgjodhi trajtimin me methimazol. Diskutohet menaxhimi i suksesshëm i orbitopatisë Graves dhe sfidat e trajtimit të strumës nodulare toxike dhe orbitopatisë Graves njëkohësisht.
**Përfundimi:** Struma nodulare toxike e shoqëruar me oftalmopati infiltrative përfaqëson shfaqjen e Semundjen së Graves, e konfirmuar nga antitrupat anti receptorë të tirotropinës. Ndërhyrja kirurgjikale konsiderohet e rëndësishme, veçanërisht në rastet kur struma nodulare toxike bashkëjeton me orbitopatinë e Graves. Artikulli nënvizon rëndësinë e një qasjeje gjithëpërfshirëse, duke përfshirë trajtimet kirurgjikale dhe mjekësore të përshtatura, për rezultate të suksesshme, në raste të tilla komplekse.



**Fjalë kyçe**: Struma nodulare hiperfunksionante, Graves' Orbitopati, carcinoma papilare e tiroides, antitrupat e receptorit të hormonit stimulus të tiroides.


## Introduction

Graves' disease (GD) may initially manifest or develop in a multinodular gland, confirmed by the presence of antibodies to the thyrotropin receptor (TSH-R Ab). Toxic nodular goiter (TNG) is rarely accompanied by infiltrative ophthalmopathy. When both conditions coexist, it typically signifies the emergence of GD (1). Several authors have historically posited that hyperthyroidism protects against thyroid cancer, asserting that the incidence of malignancy is lower in patients with TNG, compared to those with non-TNG (2-4). However, recent studies challenge this belief, reporting that the incidence of malignancy in TNG is not as low as previously thought (5- 11).
Thyrotropin-suppression therapy in euthyroid patients with thyroid autonomous functioning nodules, aimed at reducing multinodular goiter, is usually minimally effective and carries the risk of inducing thyrotoxicosis. There is no conclusive evidence that long-term thyroxine therapy alters the natural course of multinodular goiter, and randomized, placebo-controlled

trials with objective volume measurements are scarce (12- 16). Notwithstanding, approximately half of clinicians in the USA and Europe still employ this treatment. In this report, we present three cases of TNG associated with Graves' Orbitopati (GO). Remarkably, one of these cases was discovered to have papillary thyroid carcinoma (PTC) within the hyperfunctioning nodule.

**Case 1**

A 68-year-old white woman presented to our endocrinology clinic, with a 6-month history of weight loss (13 kg), nervousness, insomnia, palpitations, fatigue, tremors, and left eye complaints for two months. On physical examination: Height: 162 cm, Weight 67 kg, Blood Pressure (BP): 130/80, Tachycardia, (Pulse: 101/min, regular). Thyroid gland: Palpable nodule in the left lobe; non-suspicious lymph nodes identified clinically. Lungs and abdomen: Normal, Left Eye Examination: Proptosis, eyelid swelling, Redness of the eyelids, Mild conjunctival redness, Clinical Activity Score (CAS): 3 (0-7), Left palpable thyroid nodule, non-tender, with no suspicious lymph nodes identified clinically. Past medical history was unremarkable, with no history of neck irradiation. Family history was also unremarkable. Thyroid ultrasound revealed multiple nodules, with the dominant palpable nodule in the left lobe measuring 3.5 x 4 x 4 cm, hyperechoic with a hypoechoic halo, irregular borders, and perivascular blood flow. Additionally, two similar nodules (heterogeneous structure with irregular borders) were identified, one in the right lobe and the other in the left near the dominant nodule (Fig. 1).

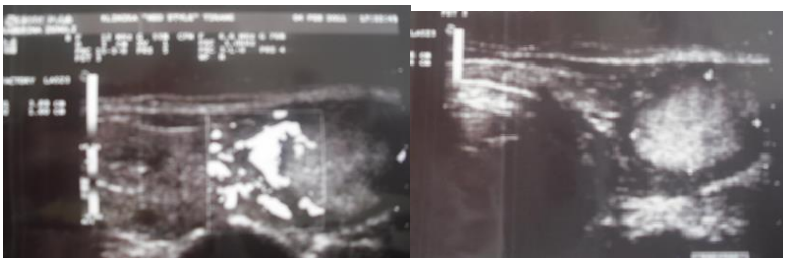

**Figure 1:** Sonogram shows a solid nodule that is hyperechoic with a hypoechoic thick halo in the left thyroid lobe, exhibiting irregular borders and perinodular blood flow.

A 99m Tc thyroid scintigraphy revealed a "hot" nodule in the left thyroid lobe and suppressed right lobe. (Fig. 2).

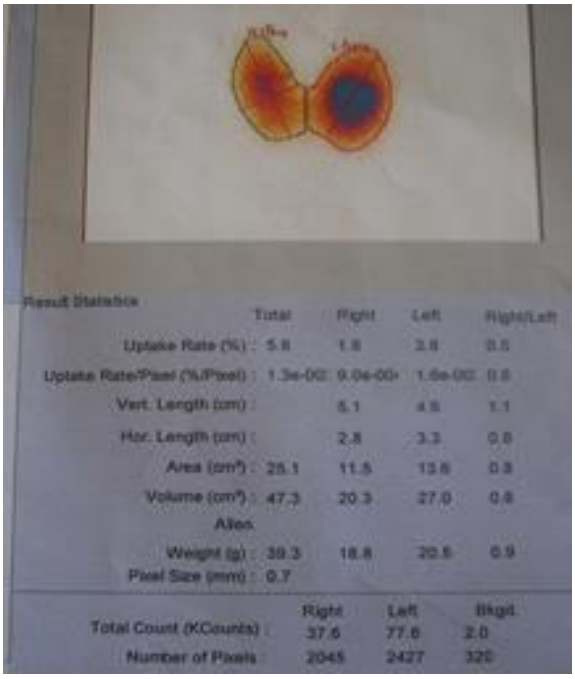


**Figure 2:** 99mTc thyroid scintigraphy reveals a "hot" nodule in the left thyroid lobe and a suppressed right lobe with high total uptake.

Assessment of thyroid functional status revealed a suppressed thyroid-stimulating hormone (TSH) <0.005 (0.27-4.2) mIU/l, free thyroxine (fT4) 21.88 (2-6.8), and TSH-R Ab 4.0 (<1) UI/ml. Treatment commenced with methimazole 40 mg daily and orally tapered prednisone 30 mg daily (0.5mg per body weight kg), along with artificial tears to protect the left eye from local damage. Once euthyroid and improved regarding eye manifestations, she underwent a total thyroidectomy. Biopsy of the dominant nodule resulted in PTC, follicular variant, and another area near the nodule with PTC Post-surgery, she started hormone replacement treatment with levothyroxine, a suppressive dose according to ATA protocols for thyroid cancer. However, four months later, she experienced a recurrence of signs and symptoms of left eye orbitopathy: inconstant diplopia, proptosis (23.5 mm in the left eye, measured using Hertel exophthalmometer), and inflammatory changes: swelling and redness of the eyelids, redness of the conjunctiva, chemosis, and pain with eye movement during the last weeks. Orbit MRI revealed enlargement of medial rectus and inferior oblique muscles, and hypertrophy of orbital fat (Fig. 3).

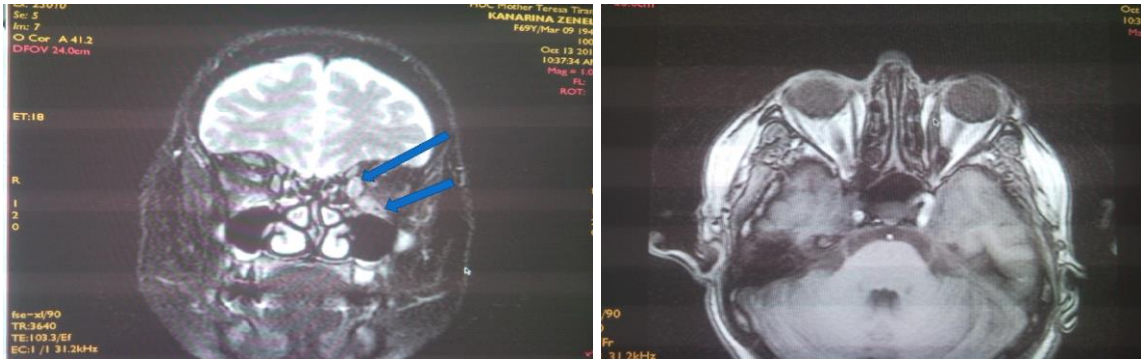

**Figure 3:** Orbit MRI revealed enlargement of medial rectus and inferior oblique muscles and hypertrophy of orbital fat.

Following the recurrence of left eye orbitopathy signs and symptoms, the patient received four intravenous pulses of glucocorticoid (a total methylprednisolone acetate dose of 2 g, 500 mg per pulse once a day over 4 days). This was administered along with local treatment, including artificial tears, lubricating cream, and sunglasses. Subsequently, she showed improvement in signs and symptoms of orbitopathy, allowing for a transition to orally taper low doses of prednisone at 30 mg daily. Two months later, a follow-up Orbit MRI revealed normal dimensions of orbit muscles with hypertrophy of orbital fat. At this point, her thyroid function tests indicated a TSH level of 1.98 (normal range: 0.27-4.2) mIU/l and TSH-R Ab 1.0 (N <1.0). She continued to maintain an euthyroid state with inconstant diplopia and inactive moderate GO. Ongoing monitoring and management were implemented to ensure sustained improvement in thyroid function and orbitopathy symptoms.

**Case 2**

A 48-year-old white woman was admitted to the Department of Endocrinology in April 2019, presenting complaints of right eye vision blurring, fatigue, palpitation, insomnia, heat intolerance, and tremors. Physical examination revealed a thyroid gland with a palpable nodule in the right lobe, no lymphadenopathy, and notable proptosis (26 mm) with inflammatory changes in the right eye. Her CAS was 6, and the left eye showed proptosis of 17 mm. Laboratory results indicated elevated FT4: 4.25 (0.75-1.70) ng/dl] and suppressed TSH 0.07 (0.27 -4.2) mIU/L. TSH-RAb 2.6 (<1) ui/l, while antithyroglobulin antibodies (anti-TG) and thyroid peroxide antibodies (anti-TPO) were negative. Thyroid ultrasonography revealed an isoechoic structure in both lobes with two nodules in the right lobe. The big one was 1.48x1.85 cm and the other of 0.85 x 0.64 cm (Fig. 4).

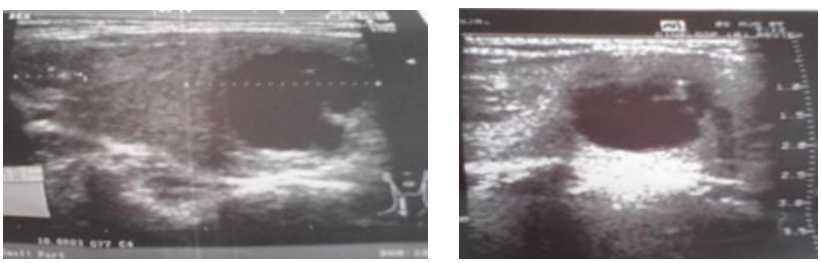

**Figure 4:** Thyroid gland images reveal the right lobe with a nodule exhibiting anechoic structure and dimensions of 1.48 x 1.85 cm, along with another heterogeneous nodule measuring 0.85 x 0.64 cm.

The 99mTc thyroid scintigraphy displays two "hot" nodules in the right thyroid lobe and suppressed left lobe, with low total uptake (Fig. 5)

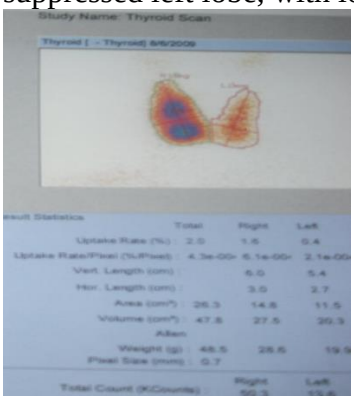

**Figure 5:** Thyroid Scintigraphy with 99m Tc, reveals two hot nodules in the right lobe and suppressed left lobe.

An orbit MRI with gadolinium documented enlargement of superior and lateral recti muscles and supraorbital soft tissues of the right eye (Fig. 6).

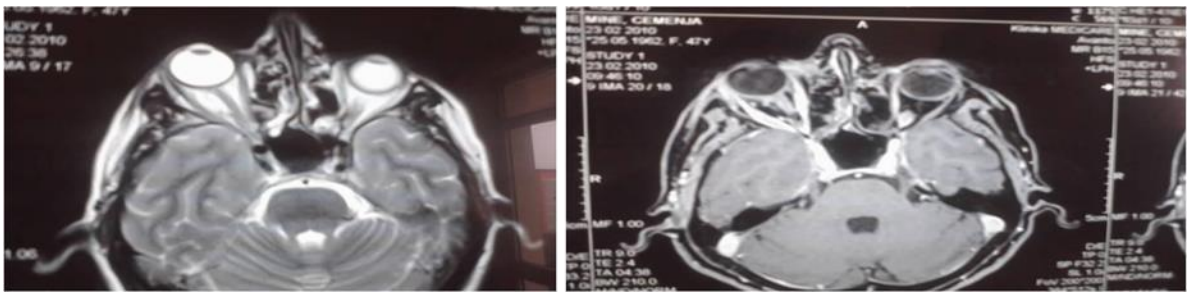

**Figure 6:** Orbit MRI reveals enlargement of lateral recti muscles of the right eye.

The patient had a history of non-TNG diagnosed 6 years ago, initially managed with levothyroxine treatment. However, after three years of therapy, she developed right eye GO associated with thyrotoxic symptoms secondary to TNG. Following evaluation, levothyroxine was discontinued, and she was initiated on 20 mg methimazole/per day and orally tapered prednisone (0.5mg per body weight kg) for GO. Despite initial improvement, a recurrence of orbitopathy symptoms led to her referral to an endocrinology service. The thyroid function tests showed a TSH of 0.868 (0.27-4.8) µIU/m, FT4 1.46 (0.75-1.70) ng/dl, and a CAS > 3 (7 points). The patient was restarted glucocorticoid therapy but intravenous pulses of methylprednisolone acetate. A total dose of 4.5 g over 12 weeks, six weeks with 500 mg intravenous per week and six weeks with 250 mg/per week (according to European Group of Graves Orbitopathy EUGOGO Protocol for GO treatment) and continuing on orally tapered prednisone (30 mg/day). Results of thyroid function tests during follow-up (Table 1).
This treatment resulted in the amelioration of eye manifestations. However, worsening eye motility and reduced visual acuity in the right eye were observed over time. Once euthyroid, the patient underwent total thyroidectomy, starting hormone replacement with levothyroxine, post-surgery. She remained euthyroid, and no detectable thyroid tissue was found on ultrasound. Histopathology examination of thyroid tissue revealed benign pathology.

**Table 1:** Results of thyroid function investigations during follow-up of case 2.

| D/M/Y | TSH (0,27-4,2mIu/l) | Ft4 (0,75-1,70) ng/dl | TSH-RAb (<1) UI/l | TPO-Ab (>75) UI/l |
|---|---|---|---|---|
| O6/09/20016 | 1,54 | 1,40 | | |
| 08/08/20019 | 0,007 | 4,25 | | |
| 11/02/2020 | 0,868 | 1,46 | | |
| 07/04/2020 | 0,07 | 4,25 | 2,6 | 19,2 |
| 06/07/2020 | 0,4 | 4,08 (7-18) pg/ml | | |
| 07/09/2020 | 0,05 | 10,4 pg/ml | | |
| 02/12/2020 | 3,74 | 5,6 pg/ml | 0,3pg/ml | |
| 21/02/2021 | 26,1 | 4,6 pg/ml | 0,9 pg/ml | 0,6 |
| 10/04/2021 | 2,04 | 13 pg/ml | | |

**Case 3**

A 53-year-old white woman presented with a year-long history of weight loss, tachycardia, and fatigue. On physical examination, both eyes exhibited proptosis (23.5 mm left eye, 24 mm right eye, measured using Hertel exophthalmometer) and inflammatory changes, with a CAS > 3. The orbit MRI revealed enlargement of the inferior, medial, and superior recti muscles (Fig. 7).

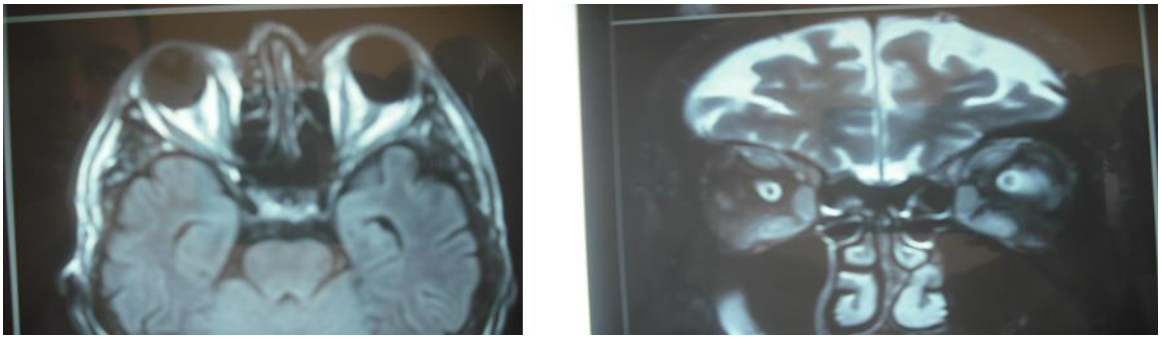

**Figure 7:** The orbit MRI revealed enlargement of the inferior, medial, and superior recti muscles.

She had a palpable nodule on the right thyroid lobe and bilateral laterocervical palpable lymph nodes, which, upon biopsy, resulted in reactive hyperplasia. Thyroid ultrasound indicated a hyperechoic nodule on the right lobe measuring 2x1.36x1.4 cm and two other hyperechoic nodules on the left lobe with dimensions over 1 cm and under 2 cm. Her 99m Tc thyroid scintigraphy showed a "hot" nodule in the right thyroid lobe and two hot nodules in the left lobe (Fig. 8).

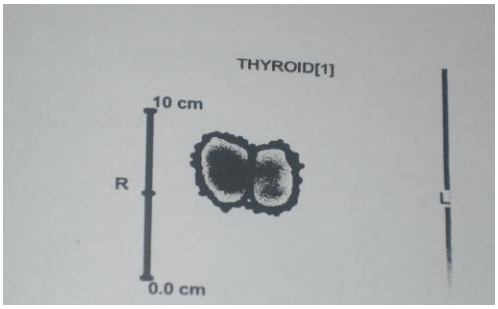


**Figure 8:** The 99mTc thyroid scintigraphy exhibits a "hot" nodule in the right thyroid lobe and two
additional hot nodules in the left lobe.

Assessment of thyroid functional status revealed a suppressed TSH <0.005 (0.27-4.2) mIU/L], elevated FT4 40.1 pg/ml (normal range 7-18)], and TSH-R Ab1.5 (<1) ui/ml. Treatment was initiated with methimazole (20 mg daily) and orally tapered prednisone (30 mg daily), along with local measures to protect the eyes. Once euthyroid and improved regarding eye manifestations, surgery was proposed as a definitive solution of hyperthyroidism. However, the patient declined, opting to continue being euthyroid under methimazole and maintaining stability regarding ophthalmopathy through local measures.

**Discussion:**

TNG accompanied by infiltrative ophthalmopathy represents the emergence of GD as confirmed by the presence of TSH-R Ab. Surgical intervention is considered a crucial therapeutic modality, especially in cases where TNG coexists with GO. We conclude by emphasizing the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in these complex cases. Discussion: The coexistence of GD with GO and PTC is considered a rare occurrence. The diagnosis of GO in our three cases was established based on the presence of ophthalmopathy, confirmed by positive serum TSH-R Ab, which are specific indicators of GD. While thyroid nodules are found in 13–20% of all GD (17), the combination of GO and TNG is infrequent, occurring in only 0.05–0.2% of patients with GD (18). Reviewing the literature indicates that incidental thyroid carcinoma in patients undergoing thyroidectomy for a hyperfunctioning nodule, both within and outside the nodule, is not uncommon. In our first patient, unilateral orbitopathy and concomitant hyperthyroidism resulted from an autonomously functioning thyroid nodule. Recent attention has been drawn to the increased risk of malignant thyroid nodules in GD patients, potentially linked to stimulating antibodies promoting cell proliferation (19,20). Consequently, optimizing the therapeutic approach in these patients becomes imperative. In our case, fine needle aspiration cytology was not performed before surgery. Total thyroidectomy was chosen for several reasons: Firstly, although cancer in TNG is rare, reported cases exist (20-22); Secondly, suspicious features on ultrasound images, including irregular borders of the dominant nodule and heterogeneous structure with irregular borders in other nodules; Thirdly, the potential exacerbation of orbitopathy with 131I therapy and finally, the absence of contraindications for surgery. Subsequent biopsy post-total thyroidectomy confirmed the coexistence of PTC in TNG,

supporting our decision for surgery as the optimal therapeutic modality in such cases. Thyrotrophin-suppression therapy in euthyroid patients with thyroid autonomous functioning nodules has limited effectiveness, carrying the risk of inducing thyrotoxicosis. In the second case, after three years of levothyroxine treatment, hyperthyroidism symptoms and unilateral GO emerged. Objective causality assessment suggested a probable relation to long-term levothyroxine use. Coexistence with unilateral orbitopathy was confirmed to be GO through the presence of TSH-R Ab. According to EUGOGO recommendations, intravenous glucocorticoids must be administered as the first-line treatment for moderate to severe and active GO. Oral glucocorticoids are considered less effective than their intravenous counterparts (23,24). Total thyroidectomy was performed due to moderate-severe orbitopathy (given that radioactive iodine treatment might worsen preexisting ophthalmopathy) and to provide a rapid and successful resolution. Post-total thyroidectomy, the patient remained euthyroid on levothyroxine treatment, reinforcing our view that surgery is the optimal therapeutic modality in similar cases.

**Conclusion:** Toxic nodular goiter accompanied by infiltrative ophthalmopathy represents the emergence of Graves' disease, confirmed by the presence of TSH-R Ab. Surgical intervention is considered a crucial therapeutic modality, especially in cases where toxic nodular goiter coexists with Graves' orbitopathy. The article underscores the importance of a comprehensive approach, including surgical considerations and tailored medical treatments, for successful outcomes in such complex cases.

**References:**


1. Williams textbook of endocrinology.eleventh edition Toxic multinodular goiter 2008;337. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6992389/.
2. Vaiana R, Cappelli C, Perini P, Pinelli D, Camoni G, Farfaglia R, et al . Hyperthyroidism and concurrent thyroidcancer. Tumori 1999; 85:247-52. [PUBMED]. https://pubmed.ncbi.nlm.nih.gov/10587026/.
3. Cole WH. Incidence of carcinoma of the thyroid in nodular goiter. Semin Surg Oncol 1991; 7 (2) 613. https://pubmed.ncbi.nlm.nih.gov/2034940/
4. Koh KB, Chang KW. Carcinoma in multinodular goitre. BrJ Surg 1992; 79 (3): 266-7. https://pubmed.ncbi.nlm.nih.gov/1555099/.
5. J Postgrad Med. 2007 Jul-Sep;53(3):157-60.Thyroid cancer in toxic and non-toxic multinodular goiter. https://www.researchgate.net/publication/6139719.
6. Gul K, Di Ri KA, Ki YG, Ersoy PE, Ugras NS, Ozdemi D, et al. Thyroid carcinoma risk in patients with hyperthyroidism and role of preoperative cytology in diagnosis. Minerva Endocrinol. 2009; 34: 281 - 288. https://pubmed.ncbi.nlm.nih.gov/20046157/.
7. Cakir M, Arici C, Alakus H, Altunbas H, Balci MK, Karayalcin U. Incidental thyroid carcinoma in thyrotoxic patients treated by surgery. Horm Res. 2007; 67: 96 - 99. https://pubmed.ncbi.nlm.nih.gov/17047344/.
8. Phitayakorn R, McHenry CR. Incidental thyroid carcinoma in patients with Graves' disease. AmJSurg. 2008; 195: 292 -297. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10118985/.
9. Alevizaki M, Papageorgiou G, Rentziou G, Saltiki K, Marafelia P, Loukari E, et al. Increasing prevalence of papillary thyroid carcinoma in recent years in Greece: the

majority are incidental.Thyroid. 2009; 19: 749 754. https://pubmed.ncbi.nlm.nih.gov/19534620/.
10. Daumerie C, Ayoubi S, Rahier J, Buysschaert M, Squifflet JP. Prevalence of thyroid cancer in hot nodules. Ann Chir. 1998; 52: 444. https://link.springer.com/article/10.1007/BF03345140.
11. Miccoli P, Minuto MN, Galleri D, D'Agostino J, Basolo F, Antonangeli L, et al. Incidental thyroid carcinoma in a large series of consecutive patients operated on for benign thyroid disease. ANZ J Surg. 2006; 76: 123 -126. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1445-2197.2006.03667.x
12. Papini E, Petrucci L, Guglielmi R, et al. Long-term changes in nodular goiter: a 5-year prospective randomized trial of levothyroxine suppressive therapy for benign cold thyroid nodules. J Clin Endocrinol Metab. 1998 83: 780-783,1998. https://pubmed.ncbi.nlm.nih.gov/9506726/.
13. Csako G, Byrd D, Wesley RA, et al. Assessing the effects of thyroid suppression on benign solitary thyroid nodules: A model for using quantitative research synthesis. Medicine 79: 9-26,2000. https://pubmed.ncbi.nlm.nih.gov/10670406/.
14. Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metab 87: 4154-4159,2002. https://www.ncbi.nlm.nih.gov/books/NBK69003/.
15. Koc M, Ersoz HO, Akpinar I, et al. Effect of low- and high-dose levothyroxine on thyroid nodule volume:acrossover placebo-controlled trial. Clin Endocrinol 57: 621-628,2002, https://pubmed.ncbi.nlm.nih.gov/12390336/.
16. Bonnema SJ, Bennedbaek FN, Wiersinga WM, Hegedus L. Management of the nontoxic multinodular goitre: a European questionnaire study. Clin Endocrinol (Oxf) 53:5-12,2000. https://pubmed.ncbi.nlm.nih.gov/10931075/.
17. Kraimps JL, BouinPineau MH, Marechaud R, et al. Basedow's disease and thyroid nodules. A common association. Ann Chir. 1998; 52: 449-451. https://pubmed.ncbi.nlm.nih.gov/9752485/
18. Smolarz K, Dederichs B, Schicha H. Simultaneous occurrence of Graves' ophthalmopathy and autonomous thyroid nodules. Nuklearmedizin. 1998; 37: 213-217. https://pubmed.ncbi.nlm.nih.gov/9770716/.
19. Papanastasiou L, Vatalas IA, Koutras DA, Mastorakos G. Thyroid autoimmunity in the current iodine environment. Thyroid. 2007; 17: 729-739. https://pubmed.ncbi.nlm.nih.gov/17725430/
20. Valenti TM, Macchia E, Pisa R, et al. Toxic adenoma and papillary thyroid carcinoma in a patient with Graves' disease. J Endocrinol Invest. 1999; 22: 701-704. https://pubmed.ncbi.nlm.nih.gov/10595835/.
21. Majima T, Doi K, Komatsu Y, et al. Papillary thyroid carcinoma without metastases manifesting as an autonomously functioning thyroid nodule. Endocr J. 2005; 52: 309-316. https://pubmed.ncbi.nlm.nih.gov/16006725/.
22. Michigishi T, Mizukami Y, Shuke N, et al. An autonomously functioning 5 thyroid carcinoma associated with euthyroid Graves' disease. J Nucl Med. 1992; 33: 2024-2026. https://pubmed.ncbi.nlm.nih.gov/1432166/.

23. Marcocci C, Bartalena L, Tanda ML et al. Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study 86: 3562-3567, 2001, https://pubmed.ncbi.nlm.nih.gov/11502779/.
24. Kahaly GJ, Pitz S, Hommel G et al. Randomized, single-blind trial of intravenous vs oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 90: 5234-5240, 2005. https://pubmed.ncbi.nlm.nih.gov/15998777/.