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# Resistance to Thyroid Hormone Complicating the Management of Papillary Thyroid Carcinoma

## Papiller Tiroid Karsinomu Yönetimini Komplike Eden Tiroid Hormon Direnci

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**Keywords:** Resistance to thyroid hormone, papillary thyroid carcinoma, TSH suppression, cervical lymph node recurrence, family screening

**Anahtar Sözcükler:** Tiroid hormonu direnci, papiller tiroid karsinomu, TSH baskılanması, servikal lenf nodu nüksü, aile taraması

***To the Editor,***

In this letter, we aim to draw attention to the clinical challenges encountered when papillary thyroid carcinoma (PTC) coexists with resistance to thyroid hormone (RTH). RTH is a rare autosomal-dominant disorder (≈1 in 40,000 births), usually due to mutations in the thyroid hormone receptor beta. It presents with elevated thyroid hormone levels and a non-suppressed thyroid-stimulating hormone (TSH) (1). Its coexistence with PTC is exceedingly rare but important, as persistently high TSH may promote tumorigenesis (2).

We present a case of a 38-year-old woman with anterior neck swelling. She was clinically euthyroid, with no family history of malignancy. Tests revealed elevated free T4 (2.11 ng/mL) and free T3 (6.25 pg/mL) with a non-suppressed TSH (3.28 µIU/mL). Autoantibodies were negative, and pituitary magnetic resonance imaging (MRI) was normal, thereby excluding TSHoma. Family screening revealed similar abnormalities in her two children, consistent with familial RTH. Neck ultrasound revealed multiple hypoechoic nodules; the largest, in the left lobe (13 × 9 × 7 mm), was cytologically classified as Bethesda V. The patient underwent total thyroidectomy with central lymph node dissection, and histopathology confirmed classical PTC (T1bN1bM0) with metastasis in the central cervical lymph nodes (Figure 1). Postoperatively, levothyroxine was initiated for TSH suppression, but despite dose escalation from 150 to 350 µg/day, TSH rose to 176.3 µIU/mL at 6 months. At 12 months, cervical recurrence was detected, requiring repeat dissection and radioiodine ablation. Following completion of surgery, the levothyroxine dose was further increased to 425 µg/day to achieve greater TSH suppression; however, due to the development of hyperthyroid symptoms, the dose was reduced to 350 µg/day, which remained the highest tolerated dose. Over the subsequent three years, TSH gradually declined (176.3 → 92.4 → 55.7 → 21.8 µIU/mL) as medication adherence improved, while free T3 and T4 levels remained within reference ranges. At her latest evaluation, serum thyroglobulin was undetectable (<0.20 ng/mL); she had no hypothyroid symptoms; and neck ultrasound revealed no pathological lymphadenopathy.

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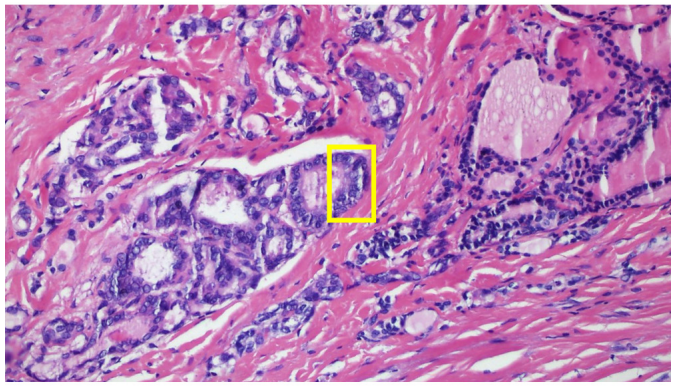

**Figure 1.** Histopatology of thyroid gland showing papillary thyroid carcinoma, classical variant: characterized by enlarged and overlapping nuclei (yellow box).

This case illustrates the difficulties in managing PTC in the setting of RTH. When free T3/T4 levels are elevated but TSH is not suppressed, the main differential diagnosis is a TSH-secreting pituitary adenoma. In our patient, the pituitary MRI was normal, supporting the diagnosis of RTH. Although genetic confirmation is recommended (3), it was not available at our center; instead, family screening supported the diagnosis.

Persistent TSH elevation despite high-dose levothyroxine is a hallmark of RTH and complicates cancer management. In our case, TSH stayed high despite >300 µg/day of levothyroxine; this is consistent with reports that suppression is rarely achievable (4), and no secondary cause, such as malabsorption or drug interactions, could explain this finding. Occasional noncompliance during the early postoperative period may also have contributed to the excessive elevation in TSH. This is clinically important, as elevated TSH may stimulate tumor growth and recurrence (2). Our patient developed regional recurrence within one year, underlining this risk. Alternative therapies such as 3,5,3'-triiodothyroacetic acid (TRIAC) can suppress TSH in RTH without causing thyrotoxic symptoms (5). However, TRIAC was not used in our case due to limited availability in our country and because biochemical improvement was gradually achieved with the maximally tolerated dose of levothyroxine alone.

The coexistence of RTH and thyroid carcinoma is exceedingly rare, with only a small number of cases described worldwide (1-3) and very few reported from Türkiye (4). Our case illustrates the practical challenges of this association, including early recurrence, difficulty achieving TSH suppression despite high-dose therapy, and the value of family screening in reaching the diagnosis. These features highlight the need for individualized care and long-term follow-up, with close monitoring for recurrence and careful adjustment of thyroid hormone therapy to balance cancer control with overall metabolic health.

### *Ethics*

**Informed Consent:** Written informed consent was obtained from the patient for publication.

### *Footnotes*

### *Authorship Contributions*

Surgical and Medical Practices: R.F.K., G.G.O., Concept: R.F.K., G.G.O., Design: R.F.K., Data Collection or Processing: R.F.K., Analysis or Interpretation: R.F.K., G.G.O., Literature Search: R.F.K., Writing: R.F.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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