ONCOLOGÍA

ISSN: 2661-6653

DOI: https://doi.org/10.33821/814
Article / Artículo

Metastasis of Solid Tumors to the Thyroid Gland: Report on Two Cases and Review

Metástasis de tumores sólidos a glándula tiroides: reporte de dos casos y revisión

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Received: 18/08/2025
Accepted: 06/11/2025
Published: 15/12/2025

ABSTRACT

Introduction: Metastases to the thyroid gland from solid malignant tumors are uncommon. They represent only 0.13–2% of thyroid neoplasms. The most common primary tumors include clear cell renal cell carcinoma, lung carcinoma, gastrointestinal carcinoma, melanoma, and, rarely, breast carcinoma. Their presentation may be metachronous, synchronous, or even its initial manifestation. Diagnosis is complex and requires immunohistochemistry (IHC), especially when the primary tumor is not evident. Given their rarity, these cases deserve scientific dissemination in Oncology and Endocrinology. **Clinical cases:** We present a male patient with stage T1N1M0 clear cell renal cell carcinoma, who presented an incidental finding of a thyroid nodule on PET-CT study resulting in thyroid gland metastasis. The second case corresponds to a female patient with stage T2N1M0 breast carcinoma with neck pain of one month duration and evidence of latero-cervical adenopathy, accompanied by thyroid micronodule. After thyroidectomy, it showed papillary thyroid microcarcinoma and metastasis to that gland from the primary tumor. **Discussion:** Thyroid metastases from solid tumors are rare. Renal carcinoma is the most frequently involved, and breast cancer the least frequent. Diagnosis requires an accurate immunohistochemical evaluation to identify the tumor origin. **Conclusion:** These cases demonstrate the importance of prolonged follow-up in cancer patients, given the risk of late thyroid metastases. Differential diagnosis and therapy should be addressed in a multidisciplinary manner, considering both the metastatic origin and the possible coexistence of primary thyroid neoplasms.

Keywords: Thyroid gland, neoplasm metastasis, Carcinoma, renal cell, metastatic breast cancer.

RESUMEN

Introducción: Las metástasis a la glándula tiroides desde tumores malignos sólidos son infrecuentes, representando solo el 0,13 a 2 % de las neoplasias tiroideas. Los tumores primarios más comunes incluyen el carcinoma renal de células claras, pulmón, gastrointestinal, melanoma y, muy raramente, de mama. Su presentación puede ser metacrónica, sincrónica o incluso como manifestación inicial. El diagnóstico es complejo y requiere inmunohistoquímica (IHQ), especialmente cuando el primario no es evidente. Dada su rareza, estos casos merecen difusión científica en oncología y endocrinología. **Casos clínicos:** Se presenta un paciente masculino con carcinoma renal de células claras con estadificación T1N1M0 que muestra un hallazgo incidental de nódulo tiroideo en estudio de PET-TC, con resultado de metástasis a glándula tiroidea, y una paciente femenina con carcinoma mamario con estadificación T2N1M0 con dolor cervical de un mes de evolución y presencia de adenopatía latero-cervical, acompañada con micronódulo tiroideo que, tras la tiroidectomía, se evidencia microcarcinoma papilar de tiroides y metástasis a dicha glándula del tumor primario. **Discusión:** Las metástasis a tiroides desde tumores sólidos son inusuales, siendo el carcinoma renal el más frecuentemente implicado y, con menor frecuencia, el cáncer de mama. El diagnóstico requiere un estudio inmunohistoquímico preciso para identificar el origen tumoral. **Conclusión:** Los casos estudiados muestran la importancia del seguimiento prolongado en pacientes oncológicos, dado el riesgo de metástasis tiroideas tardías. El diagnóstico diferencial y el tratamiento deben abordarse de forma multidisciplinaria, considerando tanto el origen metastásico como la posible coexistencia de neoplasias primarias tiroideas.

Palabras clave: glándula tiroidea, metástasis de la neoplasia, carcinoma de células renales, cáncer de mama.

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How to cite: Bautista Litardo N, Peralra Rodríguez R, Cruz Santos D & Morán Zambrano C. Metastasis of solid tumors to the thyroid gland: Report on two cases and review. Oncología (Ecuador). 2025;35(3): 26-32. https://doi.org/10.33821/814

1. Introduction

Metastases to the thyroid gland originating from solid tumors are an uncommon phenomenon that requires different prognosis, diagnostic and therapeutic strategy than primary thyroid carcinoma [1]. The main sites of origin are renal clear cell carcinoma (approximately 50%), lung adenocarcinoma, gastrointestinal neoplasms, melanoma, and breast carcinoma [2,3]. This metastatic phenomenon can occur metachronously (60%), synchronously (34%), or as the first manifestation of the underlying carcinoma (6%) [1,4].

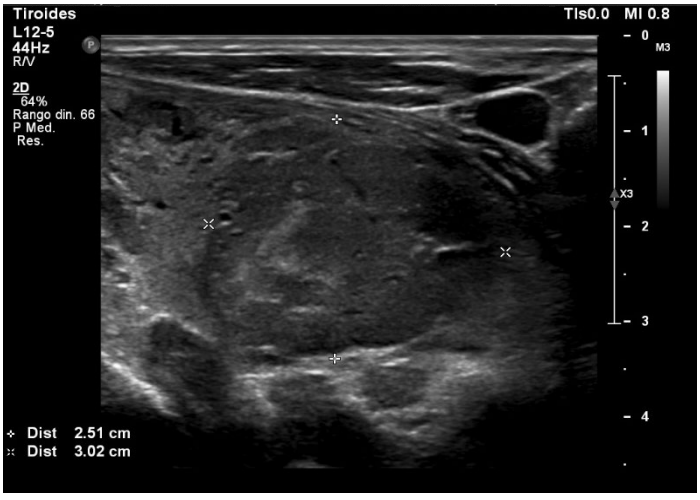
These events represent between 0.13% and 2% of all thyroid malignancies, despite the thyroid being the endocrine organ with the greatest blood supply, surpassed only by the pancreas and adrenal glands [5,6]. Hypotheses related to the high blood flow and the high iodine and oxygen content, which hinder tumor implantation and growth, have been proposed to explain its low incidence. However, pre-existing thyroid diseases such as thyroiditis, adenomas, multinodular goiter, or even primary thyroid cancer can create an environment conducive to metastatic spread [7-9].

Diagnosis presents a significant challenge, especially in the absence of a primary tumor, thus making immunohistochemistry (IHC) essential [3,4]. This series highlights metastases from renal cell carcinoma and breast cancer, which, although rare, exemplify clinically and epidemiologically relevant cases due to their diagnostic complexity and long latency periods. The average interval to the appearance of thyroid metastases is 8.8 years for renal cell carcinoma and 9 years for breast carcinoma [2,5,10]. Due to the scarcity of reports, particularly in breast cancer, this publication seeks to define and distinguish the most used diagnostic studies for these two types of malignant tumors and compare their therapeutic approach and prognosis within the fields of oncology and endocrinology.

2. Clinical case 1

We present the case of a 69-year-old man with a history of hypertension and stage III chronic kidney disease, who in 2017 underwent left radical nephrectomy for clear cell renal carcinoma (pT1bN1M0, Fuhrman histological grade III). During oncological follow-up, the patient remained asymptomatic, with a normal physical examination. A positron emission tomography (PET-CT) scan incidentally revealed a hypometabolic thyroid nodule (SUVmax [2,6]), prompting the recommendation for monitoring. Subsequently, in 2022, asymptomatic primary hypothyroidism was diagnosed without palpable findings, and treatment with levothyroxine 50 mcg/day was initiated. Two years later, a cervical ultrasound revealed a 3.5 x 2.5 x 3 cm hypoechoic solid nodule with irregular margins, cystic components, and mixed vascularization, located in the lower pole of the left lobe, classified as TIRADS 4C (Figure 1), which was palpable. A fine-needle aspiration biopsy (FNAB) of the nodule was performed and yielded a Bethesda category III.

Figure 1. Cervical ultrasound. Heterogeneous thyroid nodule measuring 3.5 x 2.5 x 3 cm.



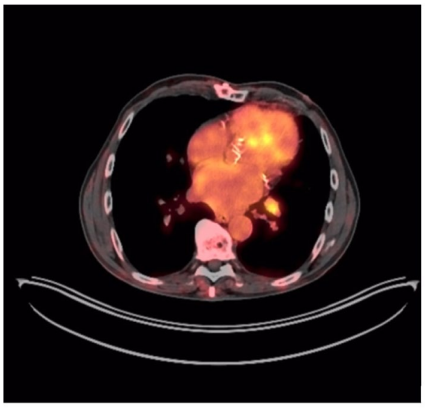
Source: SOLCA Intranet – Guayaquil.

Histopathological study of the total thyroidectomy confirmed metastasis of clear cell renal cell carcinoma, corroborated by immunohistochemistry (CAM 5.2 and PAX8 positive; thyroglobulin, CK7, and TTF1 negative). PET-CT staging identified lymphadenopathy in the left cervical region IV (23 mm, SUV LBM 4) and in the right cervical region VI (20 mm, SUV LBM 4.8).

Subsequently, the Urological Tumor Committee prescribed systemic treatment with Sunitinib 50 mg, which had to be reduced to 25 mg daily due to toxicity (hand-foot syndrome and thrombocytopenia). Following surgery, Levothyroxine was adjusted to 88 mcg/day, achieving a TSH of 0.11 µIU/mL, thyroglobulin of 0.04 ng/mL, and undetectable antithyroglobulin antibodies.

One year later, a follow-up PET-CT scan showed a decrease in the size and metabolism of cervical lymph nodes; however, a pulmonary nodule was present in the left lower lobe (13 mm), along with left hilar lymphadenopathy (12 mm), findings consistent with systemic tumor progression (Figure 2).

Figure 2. Thoracic PET-CT. Left hilar lymphadenopathy measuring 12 mm, hypermetabolic (SUV LBM 3), suggestive of metastatic origin.



Source: SOLCA Intranet – Guayaquil.

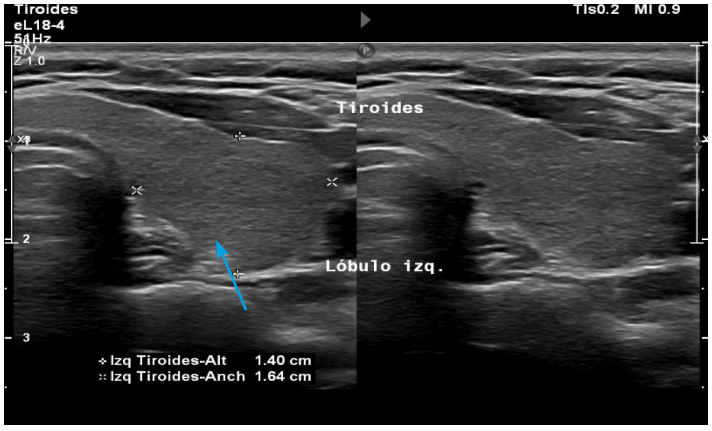
In accordance with the clinical course, second-line treatment with Axitinib 5 mg every 12 hours was initiated. As for the writing of this report, the patient remains in good general clinical condition (Functional Status Scale grade 1; Karnofsky Performance Status 90%), and under multidisciplinary follow-up.

3. Clinical case 2

A 49-year-old woman with a history of invasive ductal carcinoma of the right breast (Grade 2, HER2+++, Ki-67: 60%), with T2N1M0 in 2017, treated with six cycles of docetaxel, doxorubicin, and cyclophosphamide. In May 2021, following a one-month history of neck pain, a neck CT scan revealed lymphadenopathy in the posterior triangle (11 mm). A biopsy was taken, consistent with metastasis of the primary tumor. The patient was subsequently treated with Pertuzumab, Trastuzumab, and Docetaxel, and later continued with Letrozole 2.5 mg/day.

A PET-CT scan in December 2023 revealed persistent hypermetabolic lymphadenopathy in the left lateral cervical region (SUVmax 2.4), as well as increased metabolism in the right thyroid lobe. A cervical ultrasound in December 2024 identified a 0.69 x 0.72 cm hypoechoic solid thyroid nodule, classified as TIRADS 4A (Figure 3). The fine-needle aspiration biopsy (FNAB) was reported as Bethesda IV, and management was decided upon with close monitoring.

Figure 3. Cervical ultrasound: Thyroid nodule classified as TIRADS 4A.



Source: SOLCA Intranet – Guayaquil.

In February 2025, cervical lymph node progression and diffuse hypermetabolic activity in the thyroid were observed on PET-CT. Consequently, a total thyroidectomy with lymph node dissection was performed, revealing two distinct neoplasms: thyroid metastasis from breast carcinoma (IHC: Ki-67, HER2, PR, and GATA3 positive; TTF1 negative) and a classic papillary thyroid microcarcinoma, follicular variant pT1a pN1a, in the right lobe (0.2 cm; IHC: TTF1 and PAX8 positive).

For the microcarcinoma, ablative therapy with I-131 (180 mCi) was administered under a hormonal withdrawal protocol, with a whole-body scan showing thyroid remnants, without other iodine-sensitive lesions. Concurrently, for metastatic breast cancer, the patient continues targeted therapy with dual anti-HER2 blockade (intravenous pertuzumab and subcutaneous trastuzumab) plus oral capecitabine. At the time of data collection, the patient remains in optimal general condition (ECOG 0) and under close follow-up.

4. Discussion

Thyroid gland metastases are infrequent; renal clear cell carcinoma is the most implicated. The presence of thyroid cancer stem cells could explain this phenomenon, given their role in therapeutic resistance and invasive capacity, interacting with the tumor microenvironment and alterations in the MAPK and PI3K-Akt signaling pathways, which would favor neoplastic progression and recurrence [8,11]. This mechanism may have contributed to the clinical course of the described cases, particularly in breast carcinoma, where the coexistence of metastases promotes accelerated progression [8,12].

Likewise, the latency period between the primary tumor and thyroid metastasis is often prolonged due to the phenomenon of "metastatic dormancy," in which tumor cells remain inactive before reactivating their proliferation [11,12]. In the reported patients, thyroid metastasis was evident 7 and 8 years after the diagnosis of renal and breast carcinoma, respectively. This is consistent with the findings of Tjahjono R. et al., whose median was 92 months (7.6 years) [3,5,10]. From a diagnostic standpoint, these metastases pose a challenge, especially when the primary tumor is unknown or subclinical. Although imaging techniques are useful, they lack specificity in distinguishing between primary thyroid carcinoma and metastasis [9,11,13]. In this context, immunohistochemistry (IHC) is essential for establishing a definitive diagnosis. Specific markers, such as CD10, CA-IX, and PAX8 in renal cell carcinoma enable determining its origin. This coincides with Stergianos S. et al., who documented that 36% of metastatic thyroid tumors originated in the kidney [9,10]. In the case of breast carcinoma, the coexistence of lesions compatible with a primary thyroid tumor (TTF-1 and TG positive) and ductal carcinoma metastases (GATA3 and estrogen receptor positive) is an exceptional finding in the literature [1,6,14].

Regarding prognosis, the detection of thyroid metastases is usually associated with low 5-year survival (<50%) [5]. However, surgical resection is associated with a better outcome in cases of oligometastases, as observed in both patients who underwent total thyroidectomy and lymphadenectomy. This may be supported by a retrospective study conducted by Tjahjono R. et al. in Australia, where, although survival

was higher in patients undergoing surgery with systemic treatment (12 patients) compared to those managed only with systemic therapy/radiotherapy (3 patients) (130 vs. 36 months), it was not statistically significant (p=0.208) due to the study sample size and mortality resulting from cancer progression [1,5,6]. Furthermore, the use of tyrosine kinase inhibitors, such as Sunitinib and Axitinib has shown efficacy in tumor reduction. This aligns with the findings of Tjahjono R. et al., who demonstrated a median survival of 130 months with these drugs [3]. However, these agents are not free of complications observed with Sunitinib treatment like toxicity, notably thyrotoxicosis, gastrointestinal toxicity, and hand-foot syndrome [13]. Finally, in breast carcinoma metastases, hormonal blockade becomes relevant given the expression of receptors, which can modify the dynamics of tumor dissemination [15].

Current knowledge on thyroid gland metastases is very limited due to their rarity and the scarcity of multicenter studies. However, future lines of research are proposed, such as their application to metastasectomy in renal cell carcinoma [3] or the use of thyroid carcinoma stem cells, which interact with the tumor microenvironment, to select the most appropriate treatment, thus improving treatment outcomes and prognosis for these patients [8,11].

5. Conclusion

Thyroid metastases from solid tumors present a diagnostic and therapeutic challenge, as evidenced by the cases described. These cases underscore the importance of long-term follow-up in patients with a history of cancer due to the possibility of late recurrences or unusual metastases. Immunohistochemistry (IHC) is established as a fundamental tool for determining the tumor origin and guiding therapeutic management.

However, this series has significant limitations. By including only two cases, it is not possible to make clinical generalizations or causal inferences, which reduces external validity. Similarly, the lack of extensive clinical follow-up prevents the evaluation of long-term outcomes. Finally, the coexistence of different neoplasms in the thyroid gland highlights the biological complexity of cancer and reaffirms the need for a multidisciplinary approach.

6. Administratiev Information

6.1 Additional Files

None declared by the authors.

6.2 Acknowledgments

The authors thank the SOLCA Guayaquil staff for gathering the information provided.

6.3 Authors' Contributions

Bautista Litardo Noemi: Conceptualization, methodology, formal analysis, research, project management, drafting of the original manuscript.

Peralta Rodríguez Raúl; Cruz Santos Diego; Morán Zambrano Catalina: Conceptualization, methodology, research, visualization, drafting – revision and editing.

Both authors read and approved the final version of the manuscript.

6.4 Funding

None.

6.5 Availability of Data and Materials

Data are available upon request to the corresponding author. No other materials are reported.

7. Declarations

7.1 Ethics Committee Approval

Not required for clinical cases.

7.2 Consent for Publication

The patient's legal guardian provided written consent for the publication of this clinical case.

7.3 Conflicts of interest

The authors declare that they have no conflicts of interest or competence.

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