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Metastatic clear cell renal cell carcinoma to the thyroid gland: Case report and a brief review of the literature

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Abstract

Metastatic clear cell renal cell carcinoma (ccRCC) to the thyroid gland is an uncommon but significant presentation, often occurring years after primary tumor resection. We present the case of a 52-year-old female who developed a solitary thyroid metastasis 13 years after undergoing left nephrectomy for ccRCC. Initially presenting with a gradually enlarging neck mass and mild dysphagia, her thyroid nodule exhibited suspicious features on ultrasonography and computed tomography, including hypervascularity. Fine-needle aspiration cytology revealed clear-cell features, prompting a multidisciplinary discussion. Definitive diagnosis was established through right thyroid lobectomy and subsequent immunohistochemical analysis, which confirmed metastatic ccRCC (positive for PAX8, CD10, vimentin; negative for thyroglobulin, TTF-1).

This case is unique for its exceptionally long disease-free interval and highlights the diagnostic challenge posed by ccRCC metastases mimicking primary thyroid neoplasms. It underscores the critical importance of a thorough medical history, even for remote malignancies, and the value of comprehensive pathological and immunohistochemical evaluation in guiding accurate diagnosis and management. The patient achieved excellent long-term disease-free survival following surgical resection, reinforcing that aggressive local therapy for solitary thyroid metastases from ccRCC can lead to favorable outcomes and impact future practice by advocating for vigilant, long-term surveillance in ccRCC patients.

Keywords: Clear Cell Renal Cell Carcinoma (ccRCC); Von Hippel-Lindau (VHL); Thyroid; Metastasis; Immunohistochemical; Pathogenesis

1. Introduction

Clear cell renal cell carcinoma (ccRCC) represents one of the most prevalent and aggressive subtypes of renal malignancy, accounting for approximately 70–75% of all renal carcinoma cases. [1] This neoplasm originates from the proximal tubular epithelial cells and is. frequently associated with mutations in chromatin-modifying enzymes, including Polybromo 1, BRCA1, and SETD1. Pathogenetic mechanisms additionally involve dysregulation of the hypoxia-inducible factor (HIF) signaling cascade and alterations across multiple metabolic pathways. Environmental and genetic factors such as cigarette smoking, obesity, Von Hippel–Lindau (VHL) syndrome, and hypertension have also been identified as major contributors to ccRCC pathogenesis. [2]

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Epidemiologically, ccRCC occurs predominantly in older adults, with incidence peaking between 60 and 79 years of age and demonstrating a notable male predominance. [3] Hematogenous dissemination is the primary route of metastasis, most commonly affecting the lungs, bones, brain, liver, lymph nodes, and adrenal glands. [4] Metastatic involvement of the thyroid gland remains exceedingly uncommon, reported in only 0.2–1% of patients with ccRCC. [5]

Clinically, ccRCC typically presents with a triad of flank pain, gross or microscopic hematuria, and a palpable abdominal mass, although these features are often absent in early disease. Grossly, ccRCC lesions exhibit a yellow, solid, and cortical-based morphology, characterized histologically by cells containing abundant lipid and glycogen-rich, eosinophilic granular cytoplasm. [4] Diagnostic evaluation relies on ultrasonography and cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) to assess local and distant tumor spread. Fine-needle aspiration cytology may be employed in cases of suspected thyroid metastasis. Nevertheless, interpreting imaging studies and renal biopsies remains a diagnostic challenge. Furthermore, renal biopsy carries procedural risks including infection, hemorrhage, and arteriovenous fistula formation. [1]

Distinguishing thyroid metastases from primary thyroid carcinoma is difficult radiologically and cytologically. [5,6] Surgical management remains a subject of ongoing debate; however, total thyroidectomy is generally regarded as the optimal therapeutic approach for metastatic ccRCC to the thyroid. [**5**] Given the rarity of this metastatic pattern, the precise mechanisms facilitating renal-to-thyroid dissemination remain poorly understood. It has been postulated that the thyroid gland's unique vascular and metabolic microenvironment renders it a less favorable site for metastatic implantation. [7]

2. Case presentation

2.1. Clinical Presentation

A 52-year-old female first noticed a gradually enlarging anterior neck mass approximately eight months prior to presentation. Initially asymptomatic, she attributed it to normal physiological changes and did not seek immediate medical attention. Over the subsequent months, the nodule continued to grow, becoming more prominent and visible. She eventually developed mild dysphagia when swallowing solid foods and occasional neck discomfort. These symptoms, combined with cosmetic concerns about visible neck swelling, prompted her to consult her primary care physician. She denied any hoarseness, breathing difficulties, heat or cold intolerance, palpitations, weight changes, or other constitutional symptoms. There was no history of neck irradiation or exposure to radiation therapy.

2.2. Physical Examination and Initial Workup

Physical examination revealed a firm, mobile, non-tender thyroid nodule measuring approximately 3.5 cm in the right lobe. No cervical lymphadenopathy was palpable. The patient was clinically euthyroid with no signs of thyrotoxicosis or hypothyroidism. Initial thyroid function tests showed normal TSH, free T4, and free T3 levels. Serum thyroglobulin was within normal limits. The patient reported no significant family history of thyroid disease or endocrine malignancies. When questioned about her medical history, she mentioned only well-controlled hypertension and hyperlipidemia, both managed with medications. She did not initially disclose her prior surgical history, which was later revealed to include a left nephrectomy performed thirteen years earlier for what she described as "a kidney problem that was removed."

2.3. Radiographic Studies, Differential Diagnosis, and Cytology Findings

Thyroid ultrasonography demonstrated a 3.6 × 2.8 × 3.2 cm solid, hypoechoic nodule in the right thyroid lobe with irregular margins and increased internal vascularity on Doppler imaging. No suspicious cervical lymph nodes were identified. The left thyroid lobe appeared normal. Based on the ultrasound features, the nodule was classified as highly suspicious for malignancy (ACR TI-RADS 5).

Computed tomography (CT) of the neck with contrast revealed a heterogeneously enhancing right thyroid mass with ultrasound findings similar to those on CT. The mass showed marked enhancement during the arterial phase, which was atypical for conventional thyroid malignancies. There was no evidence of extrathyroidal extension, tracheal invasion, or pathological lymphadenopathy. The radiographic differential diagnosis included papillary thyroid carcinoma (most common), follicular thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, primary clear cell carcinoma of the thyroid (extremely rare), metastatic disease (particularly renal cell carcinoma, given the hypervascularity, though history was not initially available), and parathyroid carcinoma. The vascular enhancement

pattern raised some suspicion, but without the known history of renal cell carcinoma, primary thyroid malignancy remained the leading consideration.

Fine needle aspiration (FNA) was performed under ultrasound guidance. The cytology FNA diagnosis was "positive for malignancy with clear cell features, favor primary thyroid neoplasm, and cannot exclude metastatic disease."

2.4. Multidisciplinary Endocrine Tumor Board Meeting

The case was presented at the multidisciplinary endocrine tumor board, which included endocrinologists, endocrine surgeons, pathologists, radiologists, and oncologists. Discussion centered on the diagnostic uncertainty created by the clear cell cytology and the need for definitive tissue diagnosis. The consensus recommendation was surgical intervention with right thyroid lobectomy to obtain adequate tissue for comprehensive histopathological examination, immunohistochemical (IHC) profiling, and possible molecular studies. This approach would provide a definitive diagnosis while avoiding unnecessary total thyroidectomy if the lesion proved benign or metastatic from another primary source.

2.5. Tissue Diagnosis

Macroscopic examination of the lobectomy specimen revealed a well-circumscribed, tan-yellow, 3.8 cm mass replacing most of the right thyroid lobe. The cut surface showed a solid, friable tumor with areas of hemorrhage. Microscopically, the tumor consisted of nests and sheets of cells with abundant clear cytoplasm and well-defined cell borders, creating a characteristic "clear cell" appearance. The cells displayed centrally placed nuclei with moderate pleomorphism and conspicuous nucleoli. A delicate, arborizing vascular network was present throughout the tumor. No normal thyroid follicular architecture, colloid, papillary structures, or psammoma bodies were identified within the mass. The surrounding thyroid parenchyma showed chronic lymphocytic thyroiditis. (Figure 1 A, B, C)

The differential diagnosis at this stage included metastatic clear cell renal cell carcinoma, primary clear cell thyroid carcinoma (exceedingly rare), clear cell variant of papillary thyroid carcinoma, medullary thyroid carcinoma with clear cell features, parathyroid carcinoma, paraganglioma, and metastatic clear cell carcinomas from other sites. IHC studies revealed positive staining for PAX8, CD10, and vimentin. The tumor was negative for thyroglobulin, TTF-1, calcitonin, chromogranin, synaptophysin, PTH, and cytokeratin 7. This immunoprofile was inconsistent with any primary thyroid malignancy and definitively diagnostic of metastatic clear cell renal cell carcinoma. Upon further detailed questioning prompted by the pathology results, the patient recalled her nephrectomy thirteen years earlier, confirming the diagnosis of late metastatic disease.

2.6. Tumor Board Treatment Decision

Following the definitive pathological diagnosis, the case returned to the multidisciplinary tumor board with participation from medical oncology and radiation oncology. The pathology details of the primary renal carcinoma 13 years ago were not available. The discussion focused on staging and treatment options for metastatic renal cell carcinoma. Comprehensive staging with CT chest, abdomen, and pelvis revealed no other sites of metastatic disease; the thyroid represented isolated metastasis. Treatment options discussed included completion thyroidectomy versus observation, systemic targeted therapy, and surveillance imaging. Given the solitary nature of metastasis and complete surgical resection with negative margins, the consensus recommendation was close surveillance without immediate systemic therapy, reserving targeted agents for evidence of disease progression or development of additional metastatic sites.

2.7. Outcome and Follow-up

The patient recovered well from surgery without complications. She was followed with serial imaging, including thyroid ultrasound, chest radiography, and abdominal CT scans, initially every 3 to 6 months and then annually. At one-year post-lobectomy, she remained disease-free with no evidence of local recurrence or distant metastases. After three years, she continued under active surveillance with stable imaging and excellent performance status. At five-year follow-up, she remained without evidence of disease recurrence, maintaining normal thyroid function on levothyroxine replacement therapy. This case highlights the importance of complete medical history taking, the potential for late metastases from renal cell carcinoma even after more than a decade, and the value of surgical resection for solitary metastatic lesions. She continued regular surveillance with excellent quality of life, grateful for the thorough diagnostic workup that led to appropriate management of her unusual presentation.

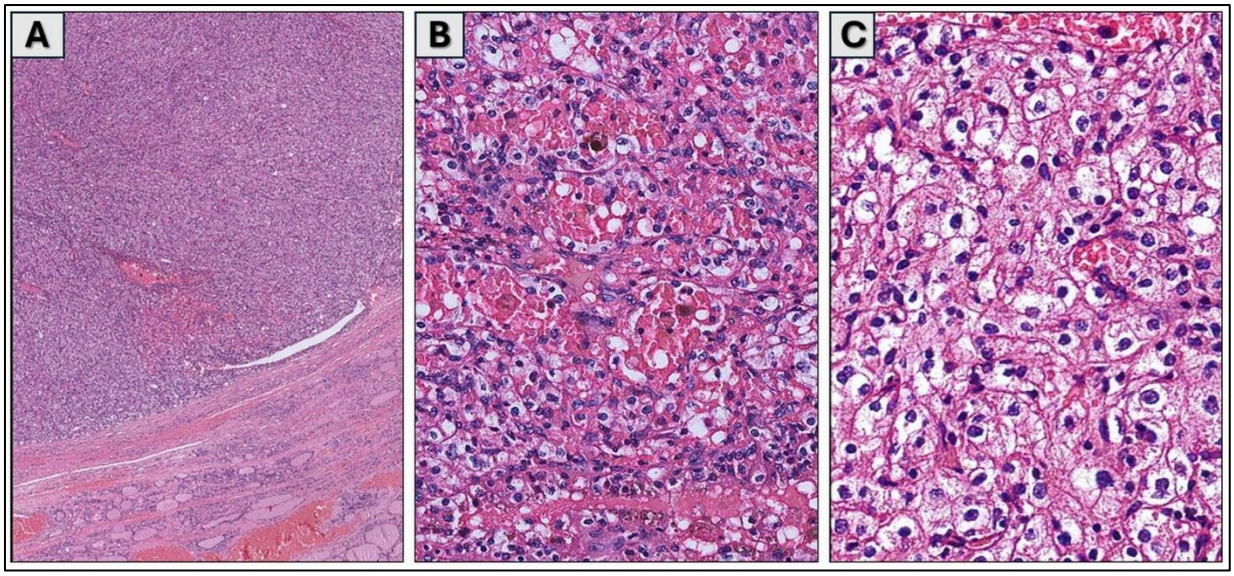

Figure 1 Microscopic examination of the excised metastatic mass of the clear cell renal cell carcinoma

- **1A:** Low power view showing well-defined metastatic mass (Upper) within the thyroid parenchyma (Lower) (HandE Stain X20).
- **1B:** Intermediate power view showing prominent tumor vascularity (HandE Stain X40).
- **1C:** High power view showing the tumor clear cell features with centrally placed nuclei, moderate pleomorphism and conspicuous nucleoli (HandE Stain X60)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, accounting for approximately 2–3% of adult cancers; clear cell RCC (ccRCC) represents nearly 70–80% of all RCC cases. [8] RCC is well known for its unpredictable metastatic behavior and its capacity to involve unusual anatomic sites, sometimes many years after treatment of the primary tumor. Among secondary malignancies to the thyroid, RCC is the most frequent primary source; however, thyroid metastases remain rare in clinical practice, comprising only 1–2% of all malignant thyroid tumors. [9,10]

Metastatic spread of RCC to the thyroid was first highlighted in a 1989 series describing patients who presented with a new palpable thyroid nodule several years after nephrectomy [4]. In affected patients, the median interval between initial RCC diagnosis and detection of thyroid metastasis is approximately 8–9 years. However, cases have been reported for more than two decades after treatment of the primary tumor. [10,11]

Clinically, thyroid involvement most often presents as a solitary thyroid nodule measuring 3–4 cm, typically in patients in their sixth or seventh decade of life. [10,12] Histologically, metastatic ccRCC within the thyroid demonstrates nests and alveolar arrangements of polygonal cells with abundant clear cytoplasm and a prominent sinusoidal vascular network. Immunohistochemistry plays a critical role in distinguishing metastatic ccRCC from primary thyroid neoplasms. Metastatic ccRCC typically expresses PAX8, CD10, and carbonic anhydrase IX (CAIX), while lacking expression of thyroglobulin and thyroid transcription factor-1 (TTF-1). [11,12]

3.2. Pathogenesis, Pathophysiology

ccRCC is characterized by early genetic events involving loss of the short arm of chromosome 3 (3p), which harbors multiple tumor suppressor genes. Loss of 3p occurs in more than 90% of both hereditary and sporadic ccRCC and represents a foundational event in tumor development. [13] This chromosomal region contains several key tumor suppressor genes, including *VHL*, *PBRM1*, *SETD2*, and *BAP1*. Among these, alterations are most frequently observed in *VHL* (~80%), followed by *PBRM1* (29–40%), *SETD2* (8–30%), and *BAP1* (6–19%). [13]

Emerging evidence suggests that chromothripsis, a catastrophic genomic event characterized by extensive chromosomal fragmentation and reassembly, may be a major mechanism underlying chromosome 3p loss in ccRCC. [14] Following 3p loss, inactivation of the remaining *VHL* allele is a critical step in tumorigenesis. Under normal physiologic conditions, the von Hippel–Lindau (VHL) protein targets hypoxia-inducible factors (HIFs) for degradation. Loss of functional VHL leads to stabilization and accumulation of HIF, resulting in constitutive activation of hypoxia-responsive genes despite normoxia. These downstream effects include increased angiogenesis via vascular endothelial growth factor (VEGF), enhanced cell proliferation via transforming growth factor-α (TGF-α), increased glucose uptake via GLUT-1, and upregulation of carbonic anhydrase IX (CAIX), thereby promoting an environment conducive to tumor growth and survival. [15]

Beyond VHL–HIF dysregulation, additional molecular pathways contribute to ccRCC pathogenesis. Alterations in the PI3K/AKT/MTOR signaling axis, through mutations in *MTOR*, *TSC1*, *PIK3CA*, or *PTEN*, are observed in approximately 20% of cases and promote cellular growth, metabolism, and survival. [16] Collectively, these molecular changes drive metabolic reprogramming, with tumor cells adopting aerobic glycolysis the Warburg effect) rather than oxidative phosphorylation, resulting in reduced mitochondrial activity. [17]

VHL inactivation also promotes lipid accumulation by increasing lipid uptake and suppressing mitochondrial fatty acid oxidation, resulting in the characteristic, abundant, clear cytoplasm seen histologically in ccRCC. [18] These metabolic and angiogenic adaptations contribute to the tumor's highly vascular nature and its propensity for hematogenous dissemination.

Therapeutically, several of these molecular pathways have emerged as important targets, including the VEGF and MTOR pathways, as well as immune checkpoints such as PD-1/PD-L1. Additional targets under investigation or incorporated into multi-kinase inhibition strategies include HIF-2α, MET, AXL, FGFR, and EGFR, with agents such as lenvatinib demonstrating activity through multi-pathway inhibition. [1,19]

Immunohistochemically, biomarkers supportive of ccRCC include CAIX (the most specific marker), CD10, vimentin, GST-α, PAX8, and RCC marker (RCCma). [1-20] Metastatic disease develops in approximately 10% of patients, most commonly involving lungs (70%), lymph nodes (45%), bone (32%), liver (18%), adrenal glands (10%), and brain (8%). [8] Metastases to atypical sites occur infrequently (<5%) and include the pancreas, pleura, peritoneum, spleen, thyroid, bowel, breast, skin, and skeletal muscle. Notably, patients with metastases to endocrine organs, such as the pancreas, thyroid, or adrenal glands, tend to have more favorable clinical outcomes despite the rarity of these presentations. [4]

3.3. Comparative analysis of our case with the existing literature. (Clinical-Radiology-Pathology, Lab, Diagnosis-Management-Outcome)

Metastatic ccRCC to the thyroid gland is a rare but well-documented phenomenon, often presenting years after primary nephrectomy. [11] The present case, involving a 52-year-old female with a 13-year interval between left nephrectomy for ccRCC and the diagnosis of a solitary thyroid metastasis, aligns with several key characteristics observed in the literature. Clinically, thyroid metastases from ccRCC frequently manifest as a gradually enlarging, asymptomatic neck mass, similar to the patient's initial presentation. [22] While primary thyroid malignancies are more common, the hypervascularity noted on imaging in this case, along with the clear cell features on fine needle aspiration (FNA), raised suspicion for metastatic disease, a diagnostic challenge frequently highlighted in reviews. [21,22]

Radiologically, thyroid ultrasound findings of a solid, hypoechoic nodule with irregular margins and increased internal vascularity are consistent with the reported features of ccRCC metastases to the thyroid. [21] These characteristics, while suspicious for malignancy, are not pathognomonic and often necessitate further investigation to differentiate from primary thyroid cancers. The computed tomography (CT) finding of a heterogeneously enhancing mass with marked arterial-phase enhancement further supported the consideration of hypervascular metastasis, a known feature of ccRCC. [6]

Pathologically, nests and sheets of cells with abundant clear cytoplasm and a delicate, arborizing vascular network are highly characteristic of ccRCC. The IHC profile, demonstrating positivity for PAX8, CD10, and vimentin, and negativity for thyroglobulin, TTF-1, and calcitonin, was crucial for definitive diagnosis. This specific immunoprofile is consistently reported as diagnostic for metastatic ccRCC, distinguishing it from primary thyroid clear cell variants or other clear cell neoplasms. [21,22] The patient's initial omission of her nephrectomy history underscores the importance of a thorough medical history in the diagnostic workup of thyroid nodules, especially when atypical features are present.

Management of solitary thyroid metastasis from ccRCC typically involves surgical resection, as performed in this case with a right thyroid lobectomy. This approach is supported by the literature, which suggests a favorable prognosis for solitary resectable metastases, with long-term survival reported after complete surgical excision. [21,24]

The patient's disease-free survival at five-year follow-up further reinforces the efficacy of this management strategy for isolated thyroid metastases. This case therefore reinforces existing knowledge of the clinical, radiological, pathological, and management aspects of ccRCC metastasis to the thyroid gland, particularly emphasizing the potential for late presentation and the diagnostic utility of IHC.

3.4. What have we learned from this case?

This case of metastatic ccRCC to the thyroid gland offers several crucial clinical insights. Firstly, it underscores the importance of a comprehensive and meticulous medical history, as the patient's initial omission of a prior nephrectomy significantly complicated the diagnostic process. Clinicians should maintain a high index of suspicion for metastatic disease in patients presenting with thyroid nodules, especially those with a history of malignancy, even if remote. Secondly, the case highlights the diagnostic challenges posed by ccRCC metastases, which can mimic primary thyroid neoplasms both clinically and radiologically. The hypervascularity observed on imaging, while atypical for many primary thyroid cancers, should prompt consideration of metastatic ccRCC, particularly in the context of clear cell features on cytology. Surgical removal of a single metastasis may lead to long-term disease-free survival, supporting aggressive local treatment for isolated metastatic ccRCC. This outcome provides valuable guidance for patient counseling and treatment planning in similar rare presentations.

Abbreviations

- Clear cell renal cell carcinoma (ccRCC);
- Von Hippel-Lindau (VHL);
- Immunohistochemical (IHC);

4. Conclusion

This case of metastatic clear cell renal cell carcinoma (ccRCC) to the thyroid gland provides several critical diagnostic lessons and reinforces key principles in oncology. Clinicians should recognize the red flag of prior malignancy history, even if distant, when evaluating new thyroid nodules, as ccRCC is notorious for late metastases. Diagnostic challenges arise from the ability of ccRCC to mimic primary thyroid neoplasms both radiologically and cytologically. Therefore, a multidisciplinary approach, integrating clinical history, imaging characteristics, and comprehensive immunohistochemical profiling, is paramount for accurate diagnosis. The successful surgical management of this solitary metastasis, resulting in long-term disease-free survival, highlights the implications for management: aggressive local therapy can be highly effective for isolated metastatic lesions.

This case reinforces the existing knowledge that while rare, thyroid metastases from ccRCC can have a favorable prognosis with appropriate intervention, challenging the notion that all metastatic disease carries a uniformly poor outlook. It also emphasizes the need for prolonged surveillance in patients with a history of ccRCC, given its propensity for delayed recurrence.

Compliance with ethical standards

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Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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