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Case Report

A Case of Tumor-to-Tumor Metastasis: Breast Carcinoma Metastatic to Oncocytic Carcinoma of Thyroid

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INTRODUCTION

Tumor-to-tumor metastasis is a rare and intriguing oncologic phenomenon in which one tumor metastasizes to the parenchyma of a separate primary tumor, which may be benign or malignant.[1] This occurrence adds complexity to cancer biology, challenging our understanding of tumor behavior, metastatic pathways, and diagnostic considerations.

In this case report, we present an instance of tumor-to-tumor metastasis involving breast carcinoma metastasizing to an oncocytic carcinoma of the thyroid. This case highlights the diagnostic challenges, clinical implications, and therapeutic considerations associated with this rare phenomenon.

CASE REPORT

A 63-year-old female was initially diagnosed with hormone receptor-positive invasive ductal carcinoma of the left breast in 2008. In December 2009, she underwent a left breast excisional biopsy, which revealed a 1.5 cm, moderately differentiated invasive ductal carcinoma with a 20% micropapillary component. The tumor was estrogen receptor (ER) positive (70%), progesterone receptor (PR) positive (7%), and human epidermal growth factor receptor 2 (HER2) negative, with an antigen Kiel 67 (Ki-67) proliferation index of 23%. Surgical margins were positive, and peritumoral lymphatic invasion was present.

In January 2010, she underwent a left breast lumpectomy, which showed no residual carcinoma. One sentinel lymph node was excised and found to contain multiple micrometastases. Her pathologic stage was T1cN1mi (T1c: tumor >1 cm but ≤2 cm; N1mi: micrometastases in axillary lymph nodes, measuring 0.2-2 mm). She completed adjuvant chemotherapy with four cycles of docetaxel and cyclophosphamide, radiation therapy to the left breast and regional lymph nodes, and six years of tamoxifen.

The patient was lost to follow-up for several years but re-established care in July 2023. At that time, she was found to have a slightly elevated cancer antigen (CA) 27.29 level. A positron emission tomography (PET) scan in September 2023 (Figure 1) revealed hypermetabolic mediastinal lymphadenopathy, sclerotic osseous metastases with mild fluorodeoxyglucose (FDG) uptake, and an avidly hypermetabolic, enlarged, nodular right thyroid gland. A bone biopsy of the right inferior pubic ramus confirmed metastatic carcinoma positive for cytokeratin 7 (CK7) and GATA-binding protein 3 (GATA3), consistent with breast origin. Due to the decalcified and crushed nature of the bone biopsy, biomarker analysis could not be performed.

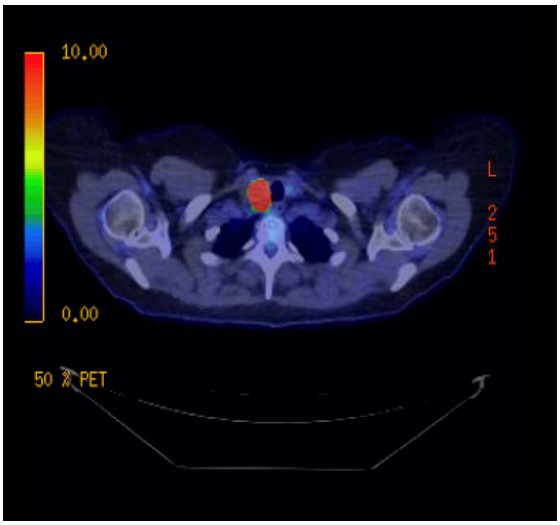

Figure 1. PET scan revealing avidly hypermetabolic right thyroid nodule.

Given her hypermetabolic mediastinal lymphadenopathy, an endobronchial ultrasound-guided fine needle aspirate (FNA) of the 11R lymph node was performed, revealing metastatic carcinoma positive for ER, GATA3, mammaglobin, and gross cystic disease fluid protein 15 (GCDFP15), and negative for thyroid transcription factor 1 (TTF1), consistent with metastatic breast carcinoma.

In November 2023, a thyroid ultrasound showed a right mid-thyroid hypoechoic nodule measuring 3.0 × 2.0 × 2.0 cm with a solid composition, categorized as TI-RADS 4 (suspicious, 5-80% malignancy). An ultrasound-guided right thyroid biopsy revealed follicular-patterned thyroid tissue without nuclear features of papillary thyroid carcinoma, leading to a differential diagnosis of thyroid follicular nodular disease or follicular neoplasm. A repeat FNA of the thyroid nodule was reported as atypia of undetermined significance. Afirma genomic sequencing classified the nodule as suspicious, with an estimated 50% risk of malignancy. *BRAF* p.V600E, *RET/PTC1*, and *RET/PTC3* mutations were not detected. She subsequently underwent a right hemithyroidectomy.

Pathology Findings. Gross examination revealed a 2.9 × 2.1 × 1.7 cm encapsulated follicular-patterned neoplasm (Figure 2). Hematoxylin and eosin (H&E)-stained sections showed an encapsulated oncocytic follicular neoplasm without nuclear features of papillary thyroid carcinoma. Foci of neoplastic follicular tumor cells were present within CD31-positive and D2-40-negative vascular spaces, confirming angioinvasion. Thus, a diagnosis of encapsulated angioinvasive oncocytic carcinoma of the thyroid was made.

Focally, involving <10% of the total nodule, was a distinct population of epithelial cells with non-oncocytic cytoplasm and a more ductal-glandular architecture. Immunohistochemistry demonstrated that these cells were strongly positive for GATA3 and ER (>95%) but negative for TTF1 and PAX8, consistent with metastatic breast carcinoma. In contrast, the adjacent oncocytic follicular epithelial cells were positive for TTF1 and PAX8 but negative for GATA3 and ER. The metastatic breast carcinoma was PR-negative and showed HER2 2+ expression by immunohistochemistry, with a nonamplified fluorescent

in situ hybridization (FISH) result.

A final diagnosis of metastatic ER-positive mammary carcinoma to an encapsulated angioinvasive oncocytic carcinoma of the thyroid was rendered. The patient was started on an aromatase inhibitor (AI) and a cyclin-dependent kinase (CDK) 4/6 inhibitor, along with a bisphosphonate for bone metastases.

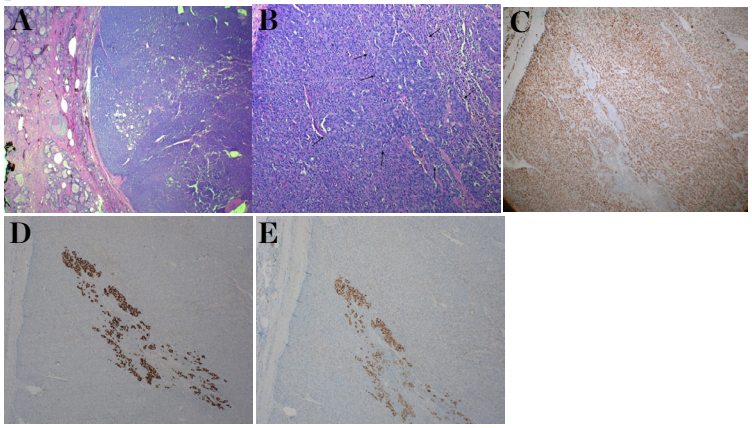

Figure 2. Metastatic breast carcinoma to an encapsulated angioinvasive oncocytic carcinoma of thyroid. A) H&E sections showed an encapsulated follicular neoplasm. B) Medium power shows a subtly distinct population of cells within the follicular neoplasm. Arrows pointing out foci of metastatic breast carcinoma. C) The second population of cells are negative for the thyroid marker PAX8 with the surrounding follicular neoplasm cells labeling as PAX8 positive. D) GATA3, and E) Estrogen Receptor (ER) are both positive in the breast carcinoma foci while the recipient thyroid neoplasm is negative for these markers.

DISCUSSION

Thyroid oncocytic carcinoma, also known as oxyphilic or Hürthle cell carcinoma, is a distinct subtype of thyroid cancer characterized by oncocytic (Hürthle) cells, which exhibit abundant eosinophilic granular cytoplasm.[2] This case represents the first reported instance of mammary carcinoma metastasizing to thyroid oncocytic carcinoma, highlighting a rare and clinically significant phenomenon: tumor-to-tumor metastasis.

Tumor-to-tumor metastasis should not be confused with a collision tumor, in which one tumor non-hematogenously invades an adjacent tumor.[3] In contrast, tumor-to-tumor metastasis is a true hematogenous process, where circulating tumor cells from a primary malignancy travel through the bloodstream and lodge in the microvasculature of a secondary tumor.

Despite its rich vascularization, the thyroid gland is an uncommon site for metastatic spread, possibly due to its high arterial flow rate. A retrospective study by Moghaddam et al.[4] found metastatic carcinoma in only 0.46% of thyroid cancer specimens, underscoring the rarity of thyroid metastasis. However, the thyroid is among the most frequently reported recipients of tumor-to-tumor metastases,[5] suggesting that thyroid tumors may create a microenvironment conducive to metastatic colonization.

Among the 150 documented cases of tumor-to-tumor metastasis in the English-language literature, 29 involved a thyroid tumor as the recipient neoplasm.[6] It is possible that disruptions in vascular architecture and alterations in blood flow within thyroid neoplasms facilitate the extravasation of circulating tumor cells, leading to the formation of metastatic deposits.

The "seed and soil" hypothesis, first proposed by Stephen Paget in 1889, suggests that the microenvironment of the host tissue (the "soil") plays a crucial role in determining the metastatic potential of circulating tumor cells (the "seeds").[7] In tumor-to-tumor metastasis, the recipient tumor's microenvironment may serve as a supportive niche for metastatic cell survival and proliferation.

Several mechanisms may contribute to this phenomenon:

- Chemotactic and homing signals: The recipient tumor may secrete cytokines, growth factors, and extracellular matrix components that attract circulating tumor cells, promoting their migration and infiltration.
- Immune evasion: Metastatic tumor cells may evade immune surveillance within the recipient tumor, enabling them to establish metastatic foci undetected.[8]
- Immunosuppressive microenvironment: Both the primary and secondary tumors may produce immunosuppressive factors, creating a tumor-permissive niche that fosters metastatic cell survival and proliferation.

Recognizing tumor-to-tumor metastasis is critical for guiding treatment decisions, as primary and metastatic tumors often have distinct biological behaviors and may not respond to the same therapies. Understanding each tumor's characteristics can inform:

- Chemotherapy and targeted therapy selection, ensuring treatments address both malignancies appropriately.
- Surgical intervention planning, where the presence of aggressive metastatic disease may necessitate prompt intervention, while a low-grade localized tumor may allow for delayed treatment.[9]
- Accurate biopsy interpretation, preventing misdiagnosis of metastatic deposits as primary malignancies.

CONCLUSIONS

This case contributes to the existing literature by documenting a unique instance of breast carcinoma metastasizing into oncocytic carcinoma of the thyroid gland. By expanding our understanding of tumor metastasis dynamics and the diagnostic challenges associated with tumor-to-tumor metastasis, we aim to improve patient outcomes and refine therapeutic strategies for similar clinical scenarios.

Increased awareness of tumor-to-tumor metastasis can prompt clinicians to consider this phenomenon in patients with multiple tumors or unexpected histological findings, ensuring comprehensive patient evaluation and appropriate management.

Overall, tumor-to-tumor metastasis is a multifaceted process driven by complex interactions between tumor cells and the host microenvironment. Elucidating the underlying mechanisms could provide valuable insights into tumor biology, potentially leading to novel therapeutic strategies that disrupt metastatic dissemination and improve patient outcomes.

REFERENCES

[1] Campbell LV Jr, Gilbert E, Chamberlain CR Jr, Watne AL. Metastases of cancer to cancer. Cancer 1968; 22(3):635-643. PMID: 5673241.
[2] Kure S, Ohashi R. Thyroid Hürthle cell carcinoma: Clinical, pathological, and molecular features. Cancers (Basel) 2020; 13(1):26. PMID: 33374707.
[3] Bulte CA, Hoegler KM, Khachemoune A. Collision tumors: A review of their types, pathogenesis, and diagnostic challenges. Dermatol Ther 2020; 33(6):e14236. PMID: 32852089.
[4] Moghaddam PA, Cornejo KM, Khan A. Metastatic carcinoma to the thyroid gland: A single institution 20-year experience and review of the literature. Endocr Pathol 2013; 24(3):116-124. PMID: 23872914.
[5] Manini C, Provenza C, Andrés L, et al. Tumor-to-tumor metastases involving clear cell renal cell carcinomas: A diagnostic challenge for pathologists needing clinical correlation. Clin Pract 2023; 13(1):288-296. PMID: 36826168.
[6] Gawlik C, Lane J, Horattas M. Tumor-to-tumor spread: A case report and literature review of renal cell carcinoma metastasis into thyroid cancer. World J Surg Oncol 2023; 21(1):362. PMID: 37990226.
[7] Akhtar M, Haider A, Rashid S, Al-Nabet ADMH. Paget's "seed and soil" theory of cancer metastasis: An idea whose time has come. Adv Anat Pathol 2019; 26(1):69-74. PMID: 30339548.
[8] Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res 2019; 79(18):4557-4566. PMID: 31350295.
[9] Patrizio A, Ferrari SM, Stoppini G, et al. Thyroid metastasis from primary breast cancer. J Clin Med 2023; 12(7):2709. PMID: 37048792.

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