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Tumor-to-tumor Metastases to Follicular Variant of Papillary Thyroid Carcinoma: Histologic, Immunohistochemical, and Molecular Studies of Two Unusual Cases

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Abstract Tumor-to-tumor metastasis in thyroid neoplasms is exceedingly uncommon. Two unusual cases of breast carcinoma and renal cell carcinoma metastatic to follicular variant papillary carcinoma are reported. On histologic sections, the donor tumor cells infiltrated the substance of the recipient tumor and the angiolymphatic channels, but the bulk of metastatic tumor was confined within the thyroid carcinoma. Immunohistochemical stains as well as molecular studies confirmed the origin of both donor tumors, as well as the diagnosis of follicular variant of papillary carcinoma in the recipient tumors. Distinguishing between two such tumor populations may be difficult when the donor tumor cells morphologically resemble primary neoplasms of the recipient organ. A history of previous malignancy and ancillary studies can be helpful in making this distinction and rendering the correct diagnosis. A brief review of literature and discussion of tumor-to-tumor metastasis in thyroid neoplasms is also presented.

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Introduction

Metastasis of one malignant tumor within the substance of another unrelated tumor (tumor-to-tumor metastasis) is distinctly uncommon. There have been less than 150 cases reported in the English literature [1]. The most frequently reported recipient tumor is renal cell carcinoma (RCC, 40–70%), followed by sarcoma, meningioma, thyroid neoplasm, and pituitary adenoma [1, 2]. In the English literature, there are only 19 cases of tumor-to-tumor metastases involving recipient thyroid neoplasms [1, 3–15]. We present two diagnostically challenging cases of tumor-to-tumor metastases that were resolved by integrating clinical, morphologic, immunohistochemical, and molecular findings.

Clinical History

Case 1 A 50-year-old woman with past medical history of a stage IIA (pT2N0M0) infiltrating lobular carcinoma of breast 10 years previously presented with a right thyroid nodule with focal intense radiotracer uptake on radioiodine scan. Fine-needle aspiration (FNA) of the nodule was consistent with a thyroid neoplasm. However, a specific type could not be classified, partly due to insufficient material for further immunohistochemical studies [16]. She subsequently underwent a diagnostic thyroid lobectomy.

Case 2 A 61-year-old man with past medical history of Furman nuclear grade III/IV, stage pT3bNxMx RCC diagnosed 3 years previously, presented with bilateral thyroid nodules. The RCC had been treated with resection followed by chemotherapy. FNA of a 6-cm dominant nodule in the right thyroid was suspicious for malignant cells. He subsequently underwent a total thyroidectomy.

Materials and Methods

Tissue specimens obtained from the thyroid lobectomy or thyroidectomy were fixed in formalin and embedded in paraffin. The paraffin-embedded sections were stained with hematoxylin-eosin for light microscopic examination.

Immunohistochemistry

Immunohistochemical studies were performed on 4-μm-thick sections of paraffin-embedded tissue, with appropriate positive and negative controls. The antibodies with their vendors, clones, and dilutions are listed in Table 1. The antibody labeling was performed with the Ventana Iview DAB (2′-diaminobenzamide) Detection Kit (DAB, Ventana Medical Systems, Tucson, AZ, USA) as the substrate chromogen (brown).

Molecular Analysis

Manual microdissection of the tissue samples was performed to include tumor tissue (T) and normal tissue (N). DNA was isolated using standard laboratory procedure. Polymerase chain reaction (PCR) was performed for the following molecular assays: (1) Three microsatellite markers (D3S1516, D3S1539, and D3S1038) were tested in loss of heterozygosity (LOH) analysis of *von Hippel–Lindau* (*VHL*) gene locus (3p25-26). (2) Twenty microsatellite markers were tested for the tumor clonality (Table 2). LOH was determined using $(N^L/N^S)/(T^L/T^S)$ formula and reported when allelic ratio for a particular marker was below 0.5 or above 2.0. From the LOH results, the likelihood ratio of common clonal origin was assessed using a calculated reliability index as described previously [17]. (3) *NRAS* codon 61 and *BRAF* gene products were amplified by PCR as described previously [18], and post-PCR melting curve analysis was used to detect possible mutations. The presence of mutation was confirmed by sequencing of the PCR product. In addition, fluorescent in situ hybridization (FISH) was performed to analyze *RET/PTC* rearrangement [19]. *RET/PTC* probe (10q11.2) and *RET/PTC1* dual-color fusion probe (10q11.2-10q21) were used. *RET/PTC* rearrangement was suggested to be present when three RET signals were identified in greater than 8% of the analyzed cells.

Results

Histologic Findings

Case 1 Microscopic examination revealed a follicular patterned neoplasm with numerous compact microfollicles of varying sizes and shapes but with nuclear features of papillary thyroid carcinoma, including nuclear enlargement, pale powdery chromatin, nuclear grooves, and intranuclear pseudoinclusions. A second population of plasmacytoid cells was interspersed between the neoplastic follicles, as well as in the angiolymphatic channels. The majority of this

Table 1 Antibodies used for immunohistochemistry

Antibody	Company	Clone	Dilution
CAM5.2	Becton-Dickinson, San Jose, CA, USA	Cam5.2	1:10
CD10	Cell Marque, Rocklin, CA, USA	56C6	Pre-diluted
CITED-1	NeoMarkers, Fremont, CA, USA	Polyclonal	1:175
ER	Ventana, Tucson, AZ, USA	SP1	Pre-diluted
Galectin-3	Vector, Burlingame, CA, USA	9C4	1:150
GCDFP	Vector, Burlingame, CA, USA	23A3	1:25
HBME-1	Dako, Carpinteria, CA, USA	HBME-1	1:100
Mammaglobin	Zeta, Sierra Madre, CA, USA	304-1A5+31A5	Pre-diluted
p53	Dako, Carpinteria, CA, USA	DO-7	1:100
p63	NeoMarkers, Fremont, CA, USA	4A4	1:200
PR	Ventana, Tucson, AZ, USA	1E2	Pre-diluted
RCC	Cell Marque, Rocklin, CA, USA	PN-15	Pre-diluted
TTF-1	Dako, Carpinteria, CA, USA	8G7G3	1:50
Thyroglobulin	Dako, Carpinteria, CA, USA	Polyclonal	1:8,000
Vimentin	Ventana, Tucson, AZ, USA	V9	Pre-diluted

Table 2 Chromosomal arms and microsatellite markers

Chromosome	Microsatellite markers
1p	D1S.162, D1S.187
1q	D1S.1183
3p	D3S.1516, D3S.1600
5q	D5S.659
9p	D9S.251
10q	D10S.1171, D10S.1173
11p	D11S.1319
12q	D12S.375
13q	D13S.319
14q	D14S.260
17p	D17S.516, D17S.768
17q	D17S.1161
18q	D18S.364
19p	D19S.401
19q	D19S.400
22q	D22S.1150

second cell population was situated within the follicular variant of papillary thyroid carcinoma (FVPTC) rather than the surrounding thyroid parenchyma (Fig. 1). No host reaction was evident around these metastatic deposits.

Case 2 On microscopic examination, the tumor had two well-demarcated components. In the center was a well-circumscribed and encapsulated mass composed of predominantly solid sheets of tumor cells with intervening delicate blood vessels. The tumor cells had moderate to abundant, predominantly eosinophilic, granular cytoplasm and pronouncedly pleomorphic nuclei with prominent nucleoli. Surrounding the poorly differentiated tumor mass, there was a minor follicular patterned component with nuclear features of papillary thyroid carcinoma (Fig. 3). The junction between these two components was abrupt with no evidence of histologic transition. No tumor was present in the surrounding normal thyroid parenchyma.

Immunohistochemical Findings

Case 1 A panel of immunohistochemical markers, including HBME1, galectin-3 (GAL3), and CITED1, was performed to confirm the diagnosis of FVPTC (Fig. 2). In contrast to the adjacent normal follicular cells and the permeating plasmacytoid cells, the tumor cells in the follicular patterned component demonstrated membranous positivity for HBME1, cytoplasmic and nuclear staining for GAL3, as well as nuclear and cytoplasmic staining for CITED1. These findings were concordant with the morphologic impression of FVPTC. The plasmacytoid cells were immunoreactive for mammaglobin, gross cystic disease fluid protein (GCDFP), estrogen receptor (ER), and progesterone receptor (PR), confirming the presence of metastatic breast carcinoma (results not shown). Thyroglobulin and thyroid transcription factor (TTF-1) staining were positive in follicular component, but negative in the plasmacytoid cells (Fig. 2). In addition, the immunostains highlighted the confinement of metastatic breast carcinoma within the FVPTC.

Case 2 The poorly differentiated major component of the tumor demonstrated no immunoreactivity for thyroglobulin or TTF-1. In contrast, the minor FVPTC component demonstrated positive immunoreactivity for both thyroglobulin and TTF-1. The poorly differentiated tumor cells were also negative for RCC antigen and p63, but were positive for CAM 5.2, CD10, vimentin, and focally positive for p53 (Figs. 3 and 4). These findings suggested either a metastatic RCC to the thyroid or dedifferentiation of the adjacent FVPTC. The histologic features and immunoprofile of the poorly differentiated carcinoma were indeterminate, and these possible diagnoses could not be definitively resolved. At the time the immunohistochemical evaluation was performed, the primary RCC case was not available for review. Therefore, a battery of molecular tests was performed to characterize the nature of the undifferentiated tumor.

Molecular Findings

Each tumor component from Case 2 was microdissected, and DNA was isolated using standard laboratory procedure. LOH analysis was performed on the poorly differentiated and FVPTC tumor components (Table 3): LOH was identified in the poorly differentiated component at loci in chromosomal regions 3p, 5q, 14q, and 17q, but not in the FVPTC component. Additionally, specific analysis at the *VHL* gene locus (3p.25-26) confirmed LOH in the poorly differentiated component only. These findings suggested with moderate reliability that these two tumor components were likely of different clonal origin. In the meantime, *NRAS* 61 mutation was identified in the FVPTC component but not the poorly differentiated component (Fig. 5b). Both tumor components were negative for *BRAF* gene mutation by PCR and *RET/PTC* rearrangements by FISH.

Follow-Up

Case 1 The patient is alive with disease at 2 years when she was noted to have metastases to bladder and pericardium, confirmed by biopsies with immunohistochemical studies. All the metastatic tumor cells showed similar plasmacytoid morphology.

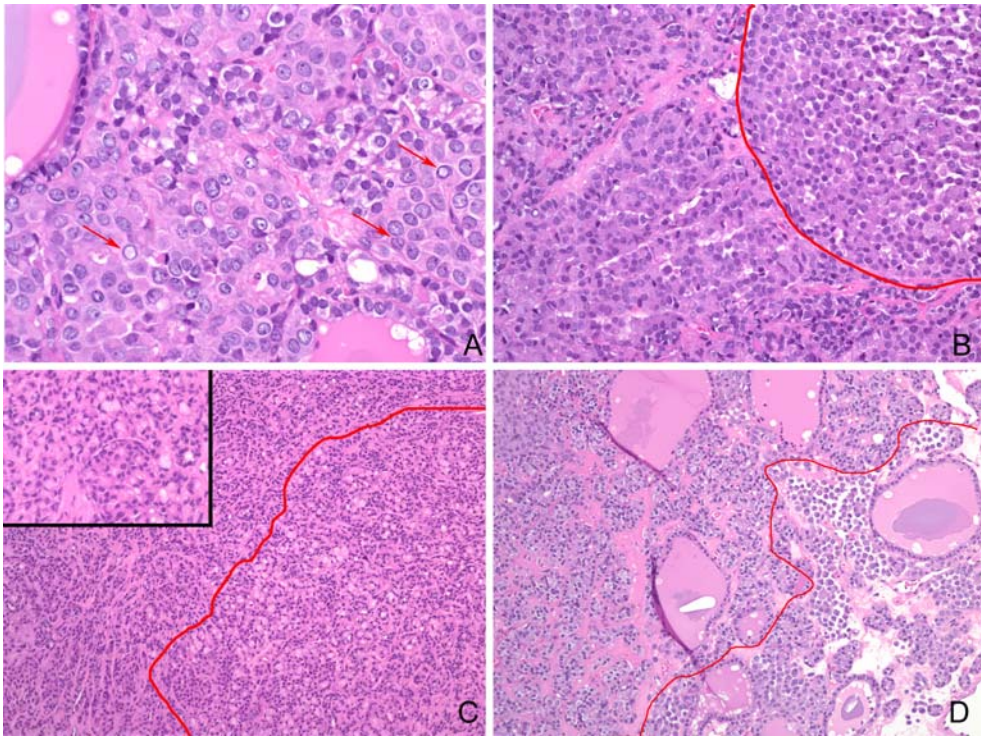

Fig. 1 Case 1, breast carcinoma metastatic to follicular variant of papillary thyroid carcinoma (FVPTC), hematoxylin-eosin stains. **a** Nuclear features of FVPTC, including nuclear enlargement, pale, powdery chromatin, nuclear grooves, and intranuclear pseudoinclusions (*arrows*). Original magnification, ×400. **b**–**d** Plasmacytoid breast carcinoma cells situated within FVPTC. Original magnifications, ×200 (**b**) and ×100 (**c**, **d**). *Inset*: high magnification image of plasmacytoid breast carcinoma cells. Original magnification, ×400

Case 2 The patient's primary RCC from 3 years ago was later obtained for review. This showed a conventional clear cell type RCC with a 20% eosinophilic granular cell component, morphologically identical to the poorly differentiated tumor component in the thyroid. He is currently alive with no evidence of disease at 1 year.

Discussion

Originally described by Berent in 1902, tumor-to-tumor metastasis is a rare phenomenon. Dobbing in 1958 and Campbell et al. in 1968 proposed a set of criteria for unequivocally documenting tumor-to-tumor metastasis [1, 4, 20, 21]: at least two primary tumors must be proved; the recipient tumor must be a true benign or malignant neoplasm; the donor tumor must be a true metastasis with established growth in the substance of the host tumor. The criteria also specifically exclude several pathologic findings that are not clearly consistent with unequivocal tumor-to-tumor metastasis: collision tumor, contiguous spread of a physically adjacent malignancy into a neighboring neoplasm, rather than the true metastasis of one malignant tumor within the substance of another tumor in tumor-to-tumor metastases; mere embolism of tumor cells without invasion into surrounding neoplastic tissue substance; and metastasis to existing hematopoietic (leukemic/lymphomatous) malignancy. Our current cases meet the strict criteria proposed by Berent and are consistent with true tumor-to-tumor metastases.

While metastases to the thyroid in general are fairly common, there have been, to our knowledge, only 19 reported actual tumor-to-tumor metastases in the English literature in which a thyroid tumor is the recipient neoplasm [3–5, 7–15, 22]. As such, it is possible that some tumor-to-tumor metastases have not been reported. The most common recipient primary tumor in thyroid gland is follicular adenoma (FA, 9/19 cases) [3, 5–9, 11, 12], followed by FVPTC (3/19 cases) [4]. Fadare et al. summarized some features shared by the majority of such cases, including multifocality of the metastatic tumor aggregates, scant reaction of the recipient tumor (desmoplastic, inflammatory, or myxoid) to the metastatic deposits, and retention of the histopathologic characteristics of the donor tumor [6].

The underlying pathogenesis of tumor-to-tumor metastasis is not well elucidated. Two major mechanisms have been widely acknowledged: anatomic/mechanical theory and metabolic ("seed and soil") theory [2, 20]. The anatomic/mechanical theory hypothesizes that rich vascularity and increased blood flow to the target organ facilitate the successful delivery and deposition of metastatic tumor cells at distant sites. The metabolic hypothesis suggests that the presence of a favorable microenvironment in the recipient tissue (the soil) favors deposition and growth of metastases (the seed). Ironically, RCC is the most common recipient site, as well as one of the most common donors, of tumor-to-tumor metastases. The increased lipid and glycogen content of RCC has been suggested as an important microenvironmental factor favoring survival of metastases to this neoplasm. RCC is also highly vascular,

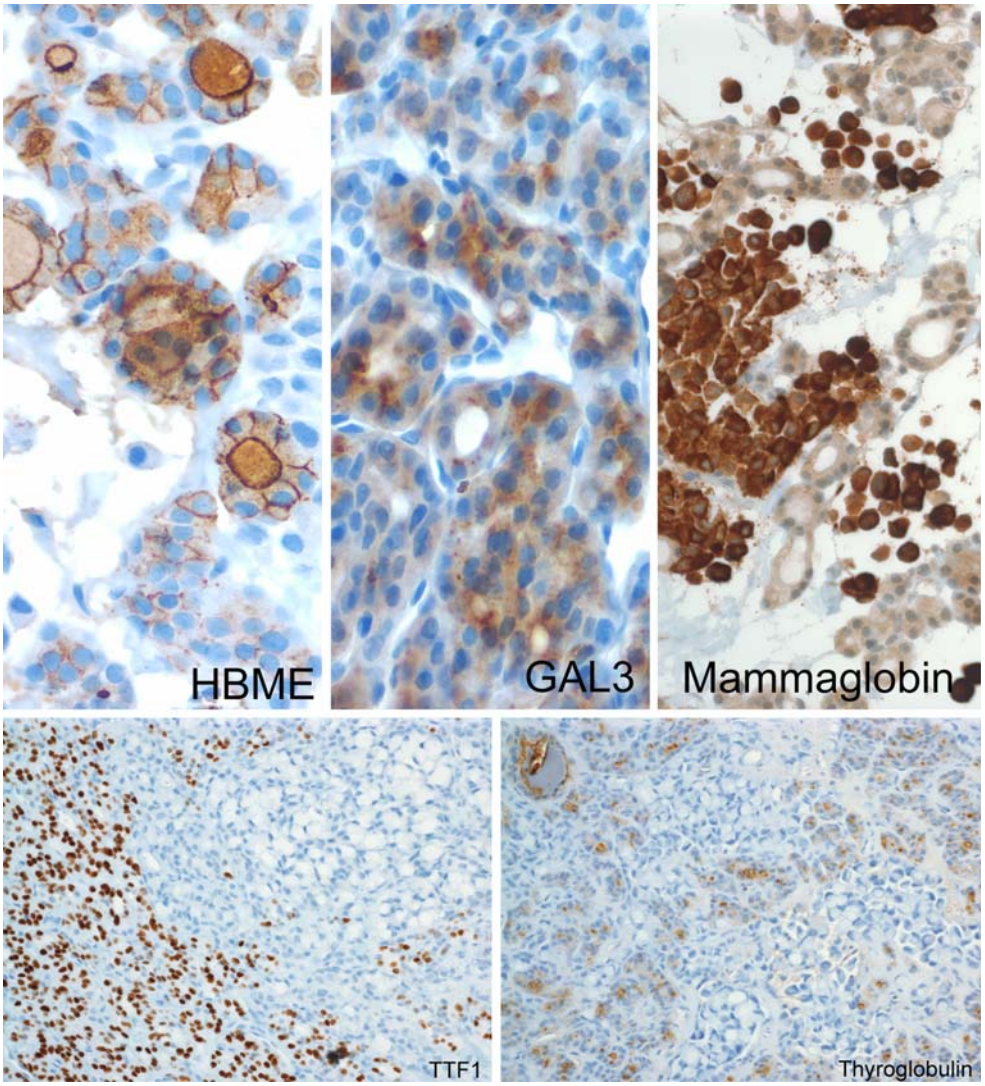

Fig. 2 Case 1, immunohistochemical stains. HBME and GAL3 show positive staining in follicular variant of papillary thyroid carcinoma (FVPTC). Mammaglobin is positive in metastatic breast carcinoma. Thyroid transcription factor (TTF-1) and thyroglobulin are positive in FVPTC as compared to negative reactivity in metastatic breast carcinoma cells. Original magnification, ×400 (HBME, GAL3, mammaglobin) and ×200 (TTF-1 and thyroglobulin)

as are the other commonly documented recipient tumors, including thyroid neoplasms.

Our series adds another two cases of tumor-to-tumor metastasis in FVPTC to existing literature describing three such cases previously reported by Baloch and LiVolsi [23]. These aggregate reports suggest that FVPTC is perhaps the most common recipient thyroid malignancy among all cases of tumor-to-tumor metastases. Baloch et al. have suggested that the increased vascularity of the thyroid gland and its primary malignancies such as PTC may favor tumor-to-tumor metastases consistent with an anatomic/mechanical hypothesis [4]. Furthermore, Giorgadze et al. recently demonstrated in their study that the intratumoral lymphatic vessel density was significantly higher in FVPTC than in either FA or follicular carcinoma [24]. It is plausible that the increased lymphovascular channels in FVPTC assist in the delivery and deposition of metastatic tumor cells within its territory. Nevertheless, whether tumor-to-tumor metastasis is only an occurrence of chance or is due to selective mechanisms unique to certain neoplasms remains controversial. Several reports have argued that the incidence of metastases to recipient tumors is the same as compared to adjacent normal parenchyma of recipient organ [6], and the donor tumors are present not only in the recipient tumors but also in the normal parenchyma of recipient organ [1, 4, 25]. However, the metastatic tumors in both cases we present were completely confined to the substance of the recipient tumors (FVPTCs), suggesting that the anatomic lymphovascular mechanism might be a valid theory of the underlying pathogenesis of tumor-to-tumor metastasis in this setting.

Both these cases were diagnostically challenging because the metastases resembled possible primary thyroid neoplasms. Both cases also demonstrated how ancillary testing can be informative in resolving this issue and proving the presence of tumor-to-tumor metastases.

In Case 1, the FNA of the thyroid contained cells from the intrathyroidal mammary carcinoma metastasis. The

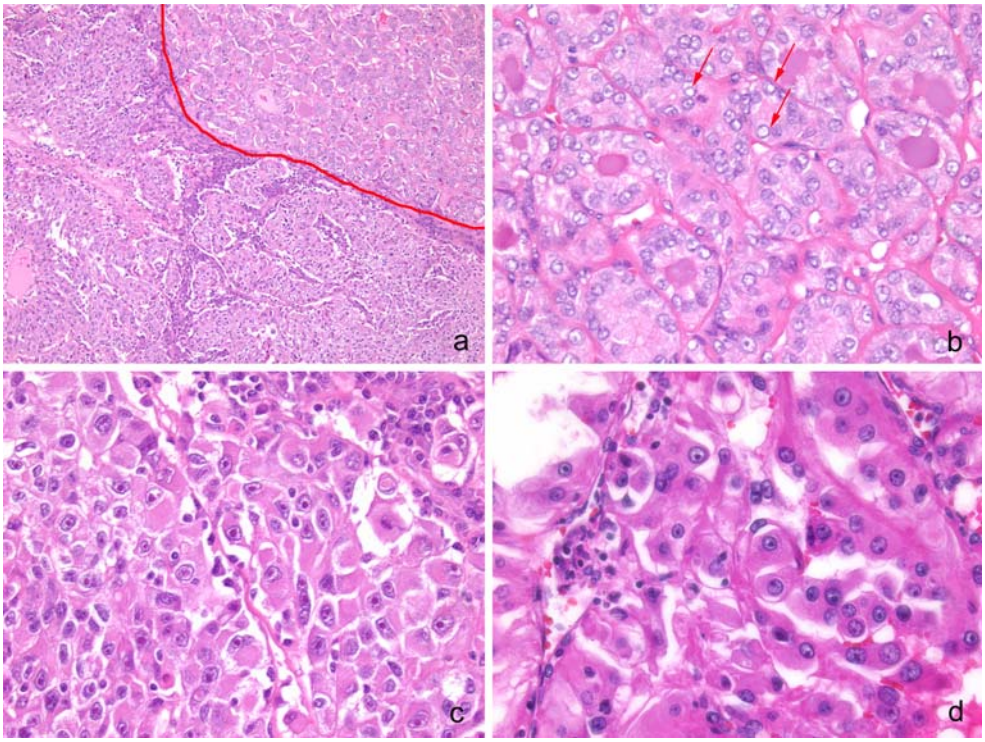

Fig. 3 Case 2, renal cell carcinoma (RCC) metastatic to follicular variant of papillary thyroid carcinoma (FVPTC), hematoxylin-eosin stains. **a** Abrupt junction between two tumor components. Original magnification, ×100. **b** Nuclear features of FVPTC, nuclear grooves, and intranuclear pseuudoinclusions (*arrows*) are present. Original magnification, ×400. **c** Metastatic RCC cells show anaplastic morphologic features. Original magnification, ×400. **d** Primary RCC cells are morphologically identical to the poorly differentiated component in the thyroid. Original magnification, ×400

plasmacytoid appearance of these cells was suggestive of medullary thyroid carcinoma [16]. The morphologic features that differentiate lobular carcinoma of breast from medullary carcinoma of thyroid may include dense, well-defined cytoplasm, dissociated cell population, as well as the lack of amorphous amyloid substance. Since the recipient tumor was so heavily colonized by the metastasis, histologic delineation between the primary and the metastatic tumor cells was difficult by light microscopy alone. Immunohistochemical stains easily resolved the two components since mammary ductal carcinoma and FVPTC typically have such contrasting immunophenotypes. Importantly, the clinical

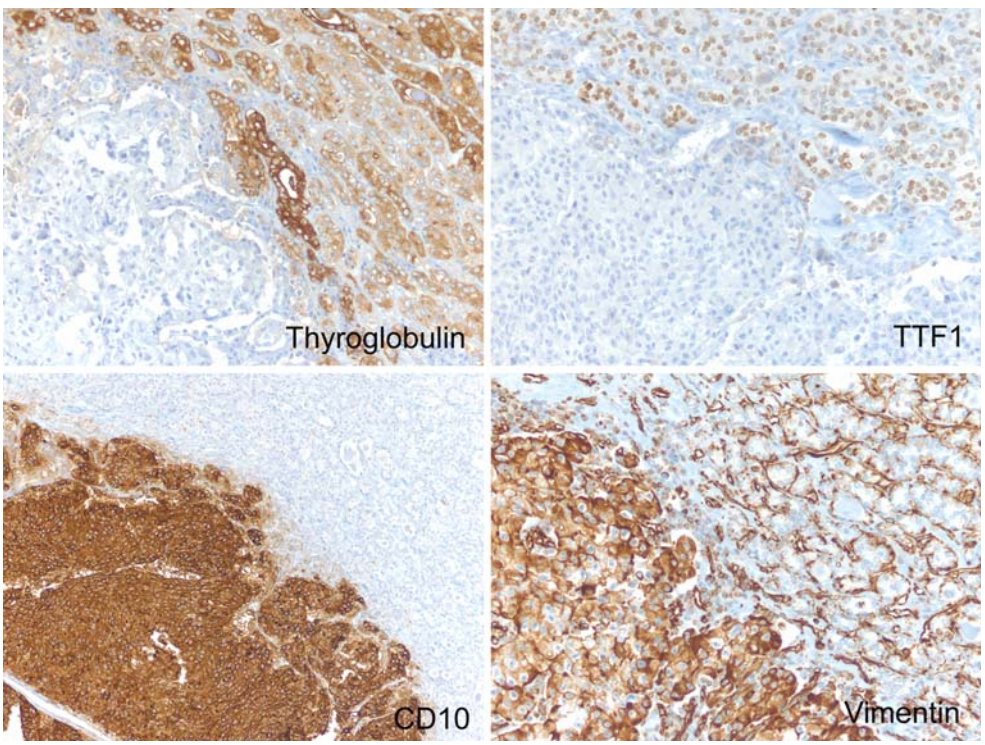

Fig. 4 Case 2, immunohistochemical stains. Thyroglobulin and thyroid transcription factor are positive in follicular variant of papillary thyroid carcinoma (FVPTC) and negative in metastatic renal cell carcinoma (RCC), while CD10 and vimentin are positive in metastatic RCC and negative in FVPTC. Original magnification, ×200

Table 3 Differential loss of heterozygosity and *NRAS* mutational profiles in two tumor components

	LOH (*VHL* locus)	LOH (3p, 5q, 14q, and 17q)	N-RAS61 mutation
T1 (FVPTC)	−	−	+
T2 (RCC)	+	+	−

history of mammary carcinoma was useful in that it prompted us to raise our index of suspicion regarding the subtle morphologic differences between the two cell populations and allowed us to focus our immunohistochemical work-up.

Case 2 presented a different set of challenges. In this specimen, both components were distinct. However, the RCC component was fairly pleomorphic and had eosinophilic appearance. Because of this unusual appearance and juxtaposition within an FVPTC, the other major diagnostic consideration was a dedifferentiation/transformation of the FVPTC. Comparison with the patient's primary material was initially not an option. The panel of immunohistochemical stains, which included CD10, vimentin, and RCC, is typically used to confirm a metastatic RCC. However, each of the stains has its limitations (i.e., the low specificity of CD10 and vimentin, and the lack of sensitivity of RCC), and none is definitive in isolation [26]. The lack of prior material, typical morphology for conventional RCC, and specific staining pattern necessitated the LOH study. This case uniquely illustrates the potential utility of molecular techniques to distinguish between tumor-to-tumor metastases and a dedifferentiated primary thyroid carcinoma. While *RAS* mutations are seen in follicular neoplasms ranging

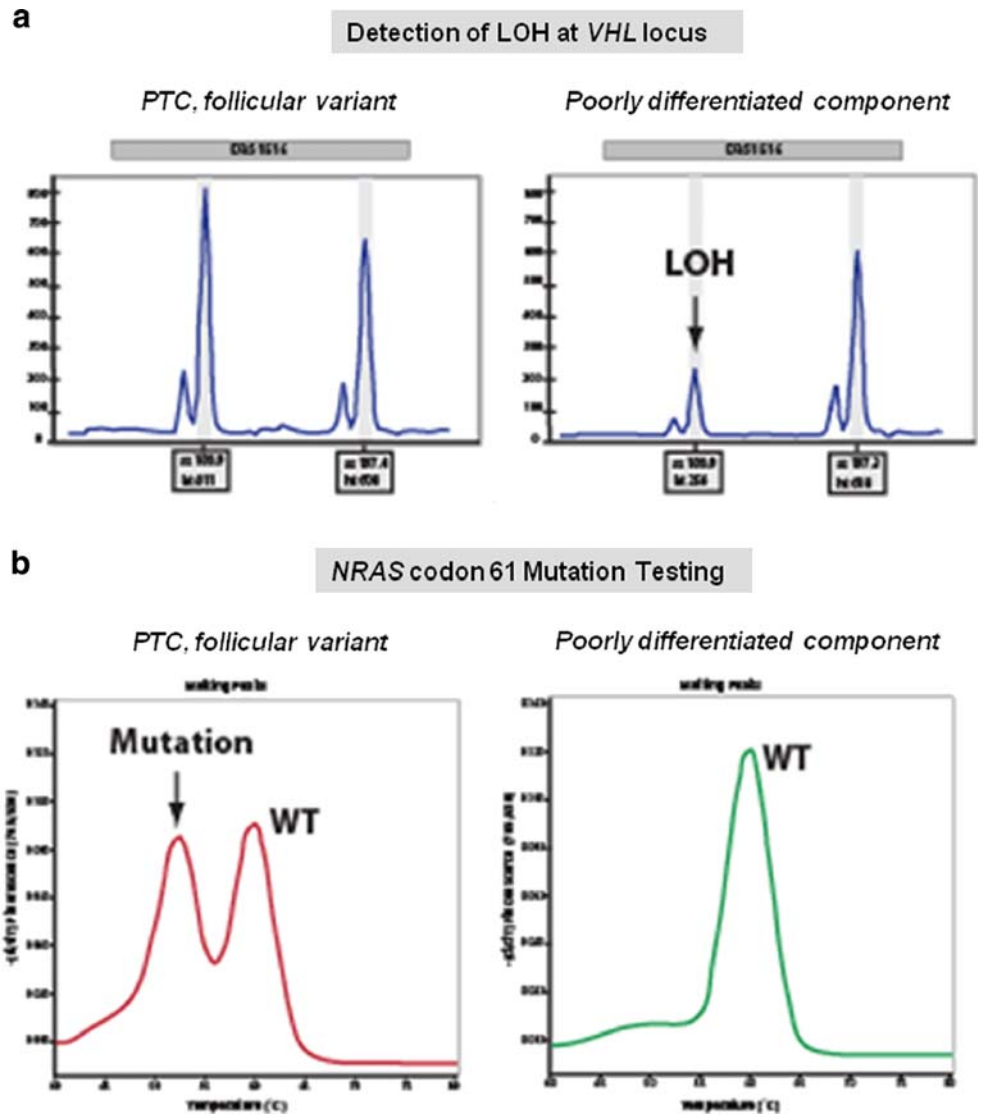

Fig. 5 Electropherograms of molecular tests. **a** Detection of loss of heterozygosity (LOH) at von Hippel–Lindau (*VHL*) locus. The poorly differentiated component showed LOH at the *VHL* gene locus (3p.25-26), while the surrounding well-differentiated follicular variant of papillary thyroid carcinoma (FVPTC) component did not. **b** Testing of *NRAS* codon 61 mutation. *NRAS* 61 mutation was identified in the FVPTC component but not in the poorly differentiated component

from FA to FVPTC, these are rare in RCC. Additionally, the *VHL* gene locus is commonly involved in RCC, but rare in follicular neoplasms other than aggressive follicular carcinomas. The distinct and different molecular profiles of the two tumor components were useful confirmatory evidence that this indeed was a tumor-to-tumor metastases rather than a focal area of dedifferentiation of the thyroid primary.

In summary, we report two cases of tumor-to-tumor metastases involving FVPTC. These cases suggest that FVPTC may be the most common malignant recipient thyroid tumor in tumor-to-tumor metastases. The biological significance of this is unclear. Morphologically, these tumors posed diagnostic challenges since the donor tumors resembled possible primary thyroid neoplasms. These ambiguities were resolved with immunohistochemical staining and differential molecular genotyping tests. Awareness of this rare and potentially problematic phenomenon and diligence in obtaining relevant clinical history and appropriate immunohistochemical and molecular testing are critical to reach a correct diagnosis and initiate appropriate therapy.

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