Metastasis of lung adenocarcinoma to follicular thyroid carcinoma combined with papillary thyroid carcinoma in the contralateral lobe: A case report

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Abstract. Cancer-to-cancer metastasis is uncommon. The present study describes a case in which lung adenocarcinoma (LC) metastasized to follicular thyroid carcinoma (FTC). A 46-year-old Chinese woman exhibited a solid carcinoma (~60x40 mm) that nearly replaced the entire thyroid tissue of the left lobe, along with papillary thyroid carcinoma (PTC) in the right lobe. The initial clinical manifestation appeared as a thyroid neoplasm. Histological examination revealed two admixed components within the neoplasm of the left lobe: FTC and an adenocarcinoma component. The mutational profile of LC was analyzed using next-generation sequencing, revealing an epidermal growth factor receptor gene mutation at exon 21 (L858R) in the LC tissue. Differentiating between two tumor populations can be challenging when donor tumor cells closely resemble primary neoplasms of the recipient organ. Beyond detailed morphological evaluation, ancillary approaches, such as immunohistochemistry and molecular testing, are essential to detect tumor-specific markers. Moreover, the degree of cell differentiation is an important determinant in diagnosing cancer-to-cancer metastasis. The present study discusses differences in tumor cell morphology and their diagnostic relevance in relation to previous reports, clinical history, histopathology and molecular pathology. The observations may contribute to improving diagnostic precision in cancer-to-cancer metastasis.

Introduction

Tumor-to-tumor metastasis is diagnosed when the recipient lesion is a true primary neoplasm and the donor lesion is an authentic metastatic deposit (1). Direct invasion of one tumor into another or the presence of isolated tumor emboli within a recipient neoplasm must be excluded from the diagnosis of tumor-to-tumor metastasis, because they do not represent true metastatic spread from the donor tumor to the recipient primary tumor but reflect local infiltration or merely the passive retention of tumor cells within the recipient tumor without the formation of lesions with metastatic biological characteristics. Tumor-to-tumor metastasis is rare (2), with <200 cases documented cases reported in the literature. Although the mechanisms of tumor-to-tumor metastasis remain unclear, proposed contributors include disruption of the vascular barrier and impaired immune surveillance within recipient thyroid lesions.

The primary malignancies that most often metastasize to the thyroid are lung carcinoma, renal cell carcinoma (RCC), colorectal carcinoma and breast carcinoma. Lung adenocarcinoma (LC, the most common subtype of lung carcinoma, frequently spreads to distant organs. Among thyroid neoplasms, follicular adenoma (FA) and papillary thyroid carcinoma (PTC) represent the most frequent benign (38%) and malignant recipients (26.5%) of metastatic tumor cells, respectively (3). The clinical presentation of thyroid metastasis is variable, typically presenting with metastatic lesions as the initial manifestation (4). Consequently, thyroid metastasis may present substantial diagnostic difficulties, with frequent misclassification as primary thyroid carcinoma.

Tumor-to-tumor metastasis involving thyroid neoplasms-particularly cases where LC affects FTC-remains rare in clinical practice, with limited evidence available to guide diagnostic and management strategies for such unusual presentations. Against this background, the primary aims of the present case report were as follows: i) To detail the clinical, imaging and pathological characteristics of a thyroid neoplasm-associated case with complex diagnostic considerations, to highlight key challenges in distinguishing secondary from primary thyroid malignancies; ii) to collate the existing literature and contextualize current understanding of tumor-to-tumor metastasis in thyroid neoplasms; and iii) provide practical insights for clinicians navigating the evaluation and management of similar cases.

Case report

A 46-year-old Chinese woman was admitted to the 960 Hospital of the Chinese People's Liberation Army in March 2020 after detection of a sizable nodule in the left thyroid lobe during a routine physical examination conducted by a general practitioner. The patient reported no pain or

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other symptoms, had no risk factors such as smoking, and no prior history of malignancy. The patient also had no family history of cancer-including thyroid cancer, lung cancer, or other malignant tumors-nor any family history of hereditary conditions. Thyroid function tests were within normal limits at presentation. Ultrasonography revealed a solid hypoechoic mass with a relatively clear margin and regular contour, measuring ~60x40 mm and occupying most of the left lobe (TI-RADS III) (Fig. S1A). However, no additional imaging beyond ultrasound (for example, CT, chest X-ray or PET) was performed preoperatively.

The patient underwent thyroidectomy with intraoperative frozen section evaluation 4 days after admission in March 2020. Histopathological analysis, performed as previously described (5), indicated an epithelial neoplasm, but its benign or malignant nature remained indeterminate (Fig. S1B). In addition, a contralateral nodule in the right thyroid lobe was definitively diagnosed as papillary thyroid carcinoma (PTC) based on intraoperative frozen section analysis, which revealed classic and unambiguous PTC features (for example, nuclear groves, powdery chromatin, and focal papillary architecture) (Fig. S1C). Due to the large size of the lesion, the suspicious left-lobe lesion, and the confirmed malignancy in the right lobe, total thyroidectomy with comprehensive neck exploration was performed. Gross examination of the surgical specimen demonstrated a solitary solid mass in the left lobe, measuring 60x40 mm, grey-red in color, firm to the touch and encapsulated by fibrous connective tissue on cut section, together with a small solid nodule, grey in color, measuring 3x2 mm, in the right lobe.

Microscopically, the solid mass in the left lobe was surrounded by a markedly thickened fibrous capsule. Serial sectioning demonstrated neoplastic cell infiltration of the capsule with focal transgression (Fig. 1A). The tumor comprised three morphologically distinct carcinoma components (Fig. 1B). The first component (T1) displayed a follicular growth pattern with medium-sized follicles containing variable amounts of colloid (Fig. 1C). The second component (T2) was characterized by solid, trabecular, or nested arrangements with only scant colloid in follicles (Fig. 1D). The third component (T3) exhibited high-grade adenocarcinoma morphology, including marked nuclear pleomorphism and prominent nucleoli, arranged in glandular, trabecular, papillary and hobnail patterns (Fig. 1E). Mitotic figures were readily observed, and tumor necrosis was evident (Fig. 1F). This component infiltrated both T1 and T2, producing indistinct boundaries between them. Immunohistochemical analysis was performed as previously described (6) and indicated that all three carcinoma components were positive for thyroid transcription factor-1 (TTF-1), cytokeratin 19 (CK19) and negative for BRAF-1, calcitonin (CT) and parathyroid hormone (PTH) (Fig. S1D-G). Both T1 and T2 showed weak CK19 expression and positivity for cluster of differentiation 56 (CD56), findings consistent with FTC rather than PTC (PTC typically demonstrates strong CK19 positivity and weak or absent CD56) (Fig. 2A and B). T1 and T2 also expressed thyroglobulin (TG) and paired box gene 8 (PAX-8), whereas T3 was negative for both these markers and CD56 (Fig. 2C and D). By contrast, NapsinA (Fig. 2E) and carcinoembryonic antigen (CEA) (Fig. S1H) were strongly expressed in T3 but absent in T1 and T2. The Ki-67 index reached 25% in T3, compared with 1% in T1 and T2 (Fig. 2F). No significant difference was observed in the cyclin D1 index across the three components, and this index was ~70% (Fig. S1I). Furthermore, all components displayed wild-type expression of P53, while the index was slightly higher in the T3 component than in the T1 and T2 component (Fig. S1J). The immunophenotypes of the three morphologically distinct carcinoma components are summarized in Table I. T1 and T2 components were classified as FTC, whereas T3 was identified as LC. The final diagnosis indicated LC metastasis to a pre-existing FTC nodule.

Table I. Immunohistochemical staining results of different tumor cell populations and the nodule in the right lobe.

Antibody	T1	T2	T3
TG	+	+	-
TTF-1	+	+	+
Napsin A	-	-	+
PAX-8	+	+	-
CK19	+	+	+
CyclinD1	+	+	+
CD56	+	+	-
BRAF-1	-	-	-
CEA	-	-	+
CT	-	-	-
PTH	-	-	-
P53	Wild-type	Wild type	Wild type
Ki-67	1%	1%	25%

-, negative; +, positive; TG, thyroglobulin; TTF-1, thyroid transcription factor-1; PAX-8, paired box gene 8; CK19, cytokeratin 19; CEA, carcinoembryonic antigen; CT, calcitonin; PTH, Parathyroid hormone; P53, Tumor protein P53; Ki-67, Ki-67 antigen.

To substantiate this diagnosis, the mutational profile of LC was analyzed using next generation sequencing (NGS). Genomic DNA was isolated from the paraffin-embedded sections using Human EGFR/KRAS/BRAF/ALK/ROS1 Genetic Test CDx (Sequencing By Reversible Terminators) kit (cat. no. KS301-FA16; Guangzhou Jinqirui Biotechnology Co., Ltd.). Fluorometric quantification was performed with the Qubit dsDNA HS Assay Kit to verify the quality and integrity of processed samples. Sequencing was performed on the Illumina MiniSeq platform using the KM MiniSeq Dx-CN Mid Output kit (300 cycles; cat. no. KS107-CXM; Guangzhou Jinqirui Biotechnology Co. Ltd.) following the manufacturer's instructions, with 2x150 bp paired-end sequencing. paired end according to the manufacturer's instructions. The final library (quantified via the Roche KAPA Library Quantification Kit) was loaded at a concentration of 1.4 pM. Sequence alignment was carried out using the Tumor Gene Data Analysis and Management System (V3; Guangzhou Jinqirui Biotechnology Co., Ltd.). The analysis revealed the L858R mutation in exon 21 of EGFR, a recognized driver mutation predominantly associated with non-small cell lung cancer (especially adenocarcinoma) and rarely observed in other tumor types. Detection of this lung-specific mutation

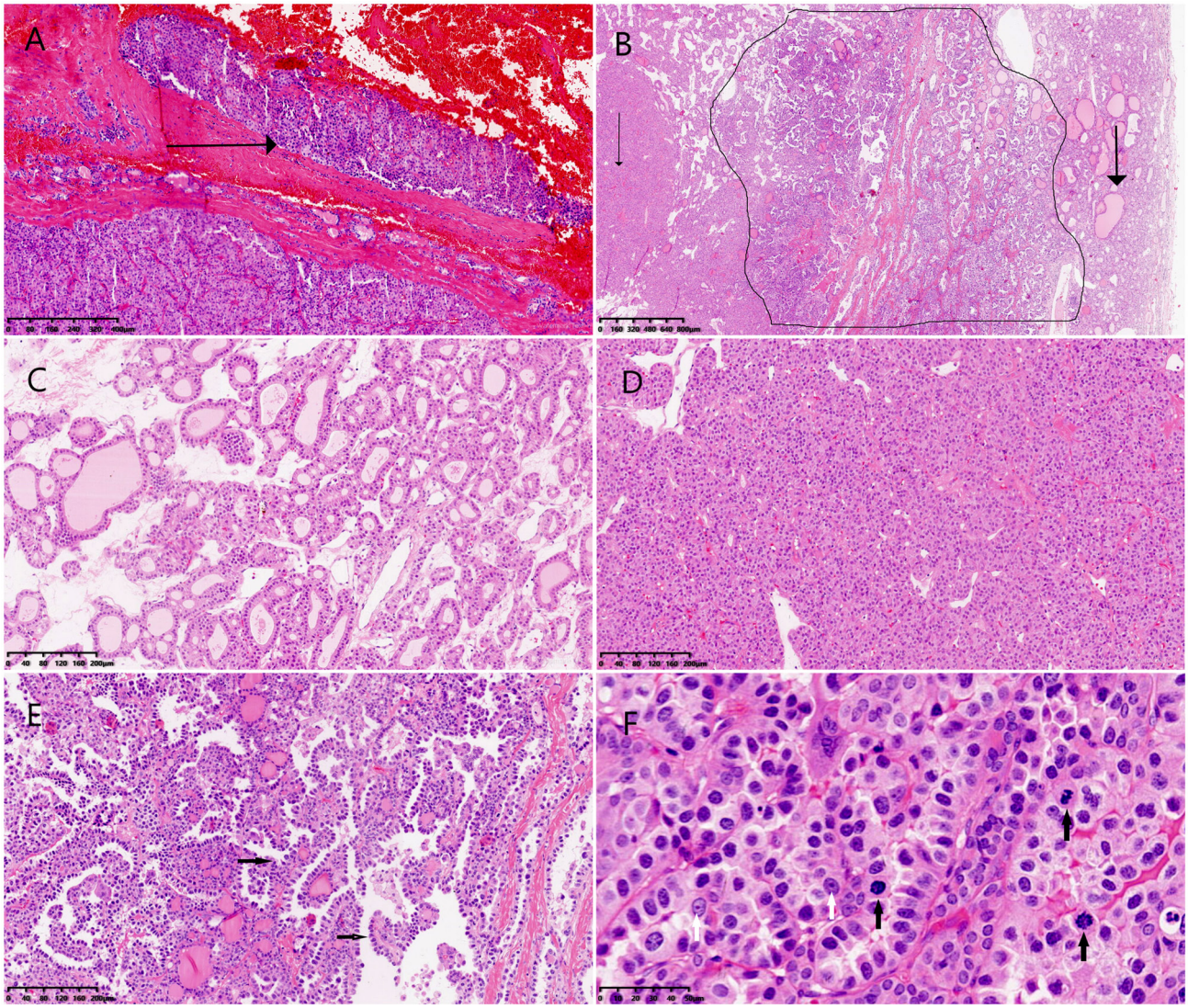

Figure 1. Microscopic examination of the recipient thyroid lesion. (A) Carcinoma was surrounded by a thickened fibrous capsule with neoplastic cells infiltrated the capsule and a focal area of penetration was identified after serial sectioning (black arrow) (H&E stain; magnification, x20). (B) Morphologically distinct components of carcinoma labeled as T1 (thick black arrow), T2 (inside the black line) and T3 (thin black arrow) (H&E stain; magnification, x20). (C) The T1 component revealed the follicular pattern features with medium size and a variable amount of colloid in the follicles when examined at a higher power, (H&E stain; magnification, x200). (D) The T2 component revealed solid, trabecular or nested growth pattern and little colloid in the follicles when examined at a higher power (H&E stain; magnification, x200). (E) T3 component revealed glandular, papillary and hobnail pattern (black arrow) when examined at a higher power (H&E stain; magnification, x200). (F) The T3 component revealed nuclear pleomorphism, conspicuous nucleoli (white arrow) and the mitotic figures (black arrow) were common (H&E stain; magnification, x400). H&E, hematoxylin and eosin.

provided strong molecular evidence for a pulmonary origin. A subsequent chest computed tomography scan revealed a 23 mm heterogeneously enhanced tumor in the left upper lobe (data not shown). Given the presence of the L858R mutation, targeted therapy with EGFR tyrosine kinase inhibitors was recommended. However, the patient declined lung biopsy and died 16 months after surgery, in July 2021.

Discussion

Tumor-to-tumor metastasis is a rare phenomenon. Garneau *et al* (3) reported four cases involving thyroid neoplasms and conducted a comprehensive literature review of English-language publications from 1962 to 2022. Since that time, to the best of our knowledge, 13 additional cases of tumor-to-tumor metastasis (3,4,7-11) (including the present case) have been documented between 2022 and 2025 (Table II). In total, 66 cases of tumor-to-tumor metastasis with primary thyroid neoplasms as recipients have been recorded, including 43 cases of cancer-to-cancer metastasis (Table III). RCC was initially regarded as the most frequent donor tumor to thyroid neoplasms (12). However, more recent data indicate that LC (16/66 cases) has become the most common donor tumor in tumor-to-tumor metastasis (Table IV), followed by renal carcinoma (15/66 cases), colon carcinoma (15/66 cases) and breast carcinoma (12/66 cases) (3,13-25). Among benign recipient tumors, FA represents the majority (20/66 cases). PTC is the most frequent malignant recipient tumor, comprising half of all reported cases (33/66). Of these 33 cases, 22 involve classic PTC and 11 involve follicular PTC. Additional recipient tumor types are listed in Table III. This distribution corresponds with the general incidence of thyroid tumors.

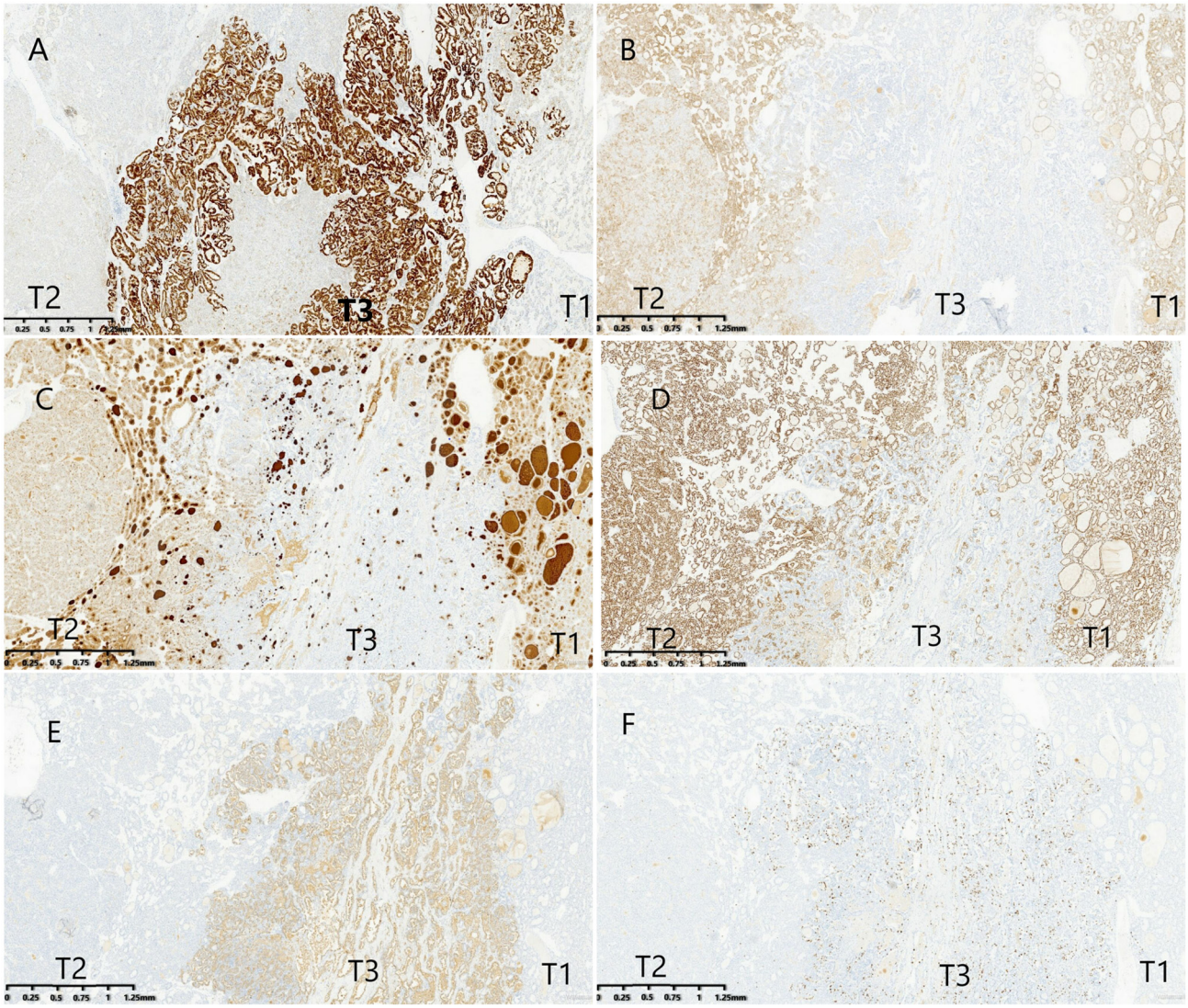

Figure 2. Immunohistochemistry examination of the three morphologically distinct components of carcinoma. (A) Both the T1 and T2 component weakly expressed CK19, whereas the T3 component was strong positive (magnification, x20). (B) Both the T1 and T2 component expressed CD56, whereas the T3 component was negative (magnification, x20). (C) Both the T1 and T2 component expressed TG, whereas the T3 component was negative (magnification, x20). (D) Both the T1 and T2 component strong expressed PAX8, whereas the T3 component was negative (magnification, x20). (E) Both the T1 and T2 component was negative for Napsin-A, whereas the T3 component was strong positive (magnification, x20). (F) The Ki-67 index was significantly higher in the T3 component than in the T1 and T2 component (magnification, x20). CK19, cytokeratin 19; CD56, cluster of differentiation 56; PAX8, paired box gene 8.

FTC is recognized as an uncommon subtype of thyroid carcinoma, accounting for 5-15% of all thyroid malignancies (26). The present report describes, to the best of our knowledge, the first case of LC metastasizing to FTC, accompanied by PTC in the contralateral lobe. This case contributes to addressing current knowledge gaps regarding LC metastasis to FTC and provides reference material for diagnostic and therapeutic considerations by clinicians and pathologists.

Metastasis to the thyroid presents considerable diagnostic challenges, often resulting in its misinterpretation as primary thyroid carcinoma (4). Tumor-to-tumor metastasis is particularly uncommon, especially when both donor and recipient neoplasms are malignant. Diagnostic imaging generally reveals no distinct clinical features or yields limited characteristic findings. In the present case, a thyroid mass represented the initial manifestation of LC. Metastatic involvement of the thyroid usually appears as a solitary lesion, which most clinical pathologists are inclined to regard as primary in origin (4). In tumor-to-tumor metastases, the metastatic component typically constitutes only a minor fraction of the donor tumor and exhibits close admixture with recipient tumor cells, without a discernible host response (desmoplastic, inflammatory, or myxoid) (1).

In the present case, LC accounted for a small portion of the FTC and demonstrated intimate intermingling with it. Although FNA remains a widely applied method for the preliminary assessment of thyroid nodules, it carries inherent limitations in detecting potential metastatic disease. The limited and fragmented nature of FNA specimens may preclude capturing the complete histological structure of a tumor, thereby restricting evaluation of growth patterns or differentiation between morphologically similar tumors, such as poorly differentiated thyroid carcinoma (PDTC)

Table II. Cases of tumor-to-tumor metastasis involving a primary thyroid neoplasm as the recipient reported from 2022 to September 2025 (n=13).

Case	Author	Publication year	Age/sex	Primary tumor	Recipient	(Refs.)
1	Garneau *et al*	2022	56/F	LC	PTC	(3)
2			76/F	BC	PTC	
3			54/F	Tonsillar SCC	PTC	
4			71/F	Colon NET	PTC	
5	Ghossein *et al*	2021	72/F	EAC	FA	(4)
6			66/F	CRC	NIEPTC	
7			65/F	RCC	NIFTP	
8	Gawlik *et al*	2023	63/F	RCC	PTC	(7)
9	Maestri *et al*	2024	70/M	HCC	HC	(8)
10	Tadisina *et al*	2024	65/M	RCC	PTC	(9)
11	Gvazava *et al*	2025	63/F	BC	HC	(10)
12	Jbali *et al*	2025	63/F	BC	PTC	(11)
13	Present case	-	46/F	LC	FTC	-

LC, lung adenocarcinoma; SCC, squamous cell carcinoma; NET, neuroendocrine tumor; EAC, esophagus adenocarcinoma; CRC, colorectal adenocarcinoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; BC, breast carcinoma; PTC, papillary thyroid carcinoma; FA, follicular thyroid adenoma; NIEPTC, non-invasive encapsulated PTC; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like; FTC, follicular thyroid carcinoma; HC, oncocytic thyroid carcinoma/hürthle cell carcinoma.

Table III. Distribution of all the 66 cases involving a primary thyroid neoplasm as the recipient in a tumor-to-tumor metastasis.

Primary tumor	Total	Recipient tumor							
		FA	PTC	FVPTC	HA	HC	FTC	MTC	NIFTP
Lung	16	7	4	4	0	0	1	0	0
Renal	15	3	5	4	1	1	0	0	1
Breast	12	3	6	1	1	1	0	0	0
Colon	15	4	7	0	0	1	1	2	0
Esophagus	1	1	0	0	0	0	0	0	0
Tonsillar	3	0	1	0	1	1	0	0	0
Pancreatic	1	0	0	1	0	0	0	0	0
Gastric	1	1	0	0	0	0	0	0	0
Prostatic	1	1	0	0	0	0	0	0	0
Liver	1	0	0	0	0	1	0	0	0
Total	66	20	22	11	3	5	2	2	1

FA, follicular thyroid adenoma; PTC, papillary thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma HA, hürthle cell adenoma; HC, oncocytic thyroid carcinoma/hürthle cell carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like.

and metastatic LC in the present case. Distinguishing primary from metastatic tumors based solely on histological characteristics remains difficult due to overlapping growth patterns. In the present study, the metastatic tumor displayed predominantly solid, trabecular, papillary or nested growth with scant colloid in follicles, leading to its initial classification as PDTC. Both PDTC and metastatic lung cancer commonly exhibit overlapping features, including solid, trabecular or nested patterns and pleomorphic cells with high nuclear-to-cytoplasmic ratios. Thus, the preliminary interpretation of the present case as encapsulated FTC with concurrent PTC and PDTC was justified. The consultant further noted that PTC (predominantly boot-spike type with some high-cell type) was embedded within FTC. The present case illustrates the diagnostic challenge posed by incomplete clinical information and highlights the importance of

Table IV. Cases of intrathyroid metastases from primary lung carcinoma (n=16).

Case	Author	Publication year	Age/sex	Primary tumor	Recipient	(Refs.)
1	Mizukami *et al*	1990	75/F	LC	FA	(13)
2	Akamatsu *et al*	1994	46/F	LC	FA	(14)
3	Baloch and Livolsi	1999	75/F	SCLC	FVPTC	(15)
4	Kameyama *et al*	2000	51/M	LC	FA	(16)
5	Mori *et al*	2008	54/M	LC	FVPTC	(17)
6	Hashimoto *et al*	2011	60/F	LC	FVPTC	(18)
7	Stevens *et al*	2011	65/M	LPDC	FA	(19)
8	Matsukuma *et al*	2013	67/F	SCLC	PTC	(20)
9	Pusztaszeri *et al*	2015	N/A	LC	FA	(21)
10	Wey and Chang	2015	64/M	SCLC	FA	(22)
11		2015	71/F	LASC	PTC	
12	Gowda *et al*	2017	52/M	SCLC	FA	(23)
13	Ozoran *et al*	2018	53/F	LC	PTC	(24)
14	Clara *et al*	2022	70/M	LCC	FVPTC	(25)
15	Garneau *et al*	2022	56/F	LC	PTC	(3)
16	Present case	-	46/F	LC	FTC	-

NA, not available; LC, lung adenocarcinoma; SCLC, lung small cell carcinoma; LPDC, lung poorly differentiated carcinoma; LASC, lung adenosquamous carcinoma; LCC, lung carcinoid; FVPTC, follicular variant of papillary thyroid carcinoma.

considering tumor-to-tumor metastasis when a lesion demonstrates a bimorphic appearance with distinct morphological components.

Although the present case posed diagnostic challenges, tumor-to-tumor metastasis should be considered whenever atypical cytological and histological features are encountered. In this instance, as metastatic deposits largely preserved the morphology of the primary tumors, accurate identification was possible. The metastatic tumor partially resembled primary PDTC but also exhibited characteristics of a high-grade adenocarcinoma, including marked nuclear pleomorphism, prominent nucleoli and necrosis, suggesting the likelihood of metastasis. Immunohistochemical staining resolved these diagnostic uncertainties. In this report, immunostains for TG, PAX-8, TTF-1, CEA and NapsinA proved valuable in differentiating primary thyroid carcinoma from metastatic LC. PDTC, a follicular-derived primary thyroid tumor, showed positivity for TG, PAX-8 and TTF-1, but negativity for NapsinA and CEA. By contrast, the metastatic adenocarcinoma demonstrated positivity for TTF-1, NapsinA and CEA, with negativity for TG and PAX-8. The Ki-67 index was considerably higher in the adenocarcinoma component (25%) compared with the FTC component (1%). Pathological evaluation was performed using stains specific to both thyroid and lung origins. TTF-1, although expressed in tumors of both sites, has limited diagnostic value without additional markers such as Napsin A and TG. In diagnostically complex cases, molecular testing can be informative, as tumor-specific mutations and rearrangements (for example, BRAF V600E, EGFR, ALK and ROS) help determine the site of origin (12). The mutational spectrum of LC was further examined with NGS, which revealed the L858R substitution in EGFR exon 21. This well-characterized driver mutation, strongly associated with non-small cell lung cancer (particularly adenocarcinoma) and uncommon in other malignancies, provided compelling molecular evidence for the pulmonary origin of the metastatic component (27). Recognition of tumor-to-tumor metastasis should be considered when bimorphic structure and divergent morphologies are encountered. Accurate diagnosis requires the application of appropriate immunohistochemical markers and molecular assays, which also guide the selection of targeted therapeutic strategies.

Malignant tumors with distant metastasis generally carry a poor prognosis. The role of surgical resection in thyroid metastasis has been widely debated in the literature. Current evidence indicates that removal of isolated thyroid metastases yields superior survival compared with conservative management, with subsite analyses highlighting benefits particularly for metastases originating from the kidney, colon or lung (6,28,29). Ghossein *et al* (4) reported that surgical intervention with curative intent may be appropriate in cases of oligometastasis to the thyroid gland, potentially improving survival and even achieving long-term remission. Accordingly, surgical treatment is advised for solitary metastatic lesions (30). Surgical decision-making additionally depends on factors such as the histological subtype of the primary tumor, anatomical location of the intrathyroid metastasis, biological behavior of the primary malignancy, and classification of metastasis as oligometastatic or polymetastatic. For patients with metastasis, targeted therapy represents an effective treatment strategy, with drug selection guided by specific genetic alterations (BRAF V600E, EGFR, ALK, ROS and others). In the present case, no

evidence of metastasis was detected outside the thyroid, and surgical excision of the metastatic tumor was achieved. Given the presence of the L858R mutation, targeted therapy with EGFR tyrosine kinase inhibitors was advised. However, the patient declined lung biopsy and subsequent therapy, and died 16 months after surgery.

In conclusion, to the best of our knowledge, the present case represents the first report of LC metastasizing to FTC with concurrent PTC in the contralateral lobe. It illustrates the diagnostic challenge encountered in the absence of a prior clinical history of malignancy and stresses the necessity for pathologists to maintain strong suspicion for cancer-to-cancer metastasis when a tumor exhibits bimorphic structure and distinct morphological characteristics. Considering the markedly poor prognosis associated with metastatic tumors, early and accurate diagnosis remains essential for timely and appropriate management. Despite the generally unfavorable outcome, surgical intervention in selected patients with metastases may contribute to improved survival.

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Availability of data and materials

All original NGS data generated in this study have been deposited in the Sequence Read Archive database of the National Center for Biotechnology Information (accession no. SRR35762829; https://www.ncbi.nlm.nih.gov/sra). The rest of the data generated in the present study may be requested from the corresponding author.

Authors' contributions

CW and XL acquired the data. CW, YY, LB and XL analyzed and interpreted the data and confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures complied with applicable laws and institutional regulations and were approved by the relevant institutional committee.

Patient consent for publication

The privacy rights of the subject were respected, and waiver of informed consent was obtained for participation and publication.

Competing interests

The authors declare that they have no competing interests.

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