

## CASE REPORT

# A patient with a rare co-occurrence of papillary and follicular thyroid carcinomas

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## Key Clinical Message

The occurrence of papillary and follicular thyroid carcinoma as a collision tumor is rare. We report on a case of a collision tumor consisting of papillary and follicular thyroid carcinoma treated successfully with surgery and radioiodine ablation.

## KEYWORDS

ear/nose/throat, endocrinology and metabolic disorders, oncology, surgery

## 1 | BACKGROUND

Collision tumors are defined as two histologically and structurally distinct malignancies within the same organ.<sup>1</sup> These tumors are extremely rare and account for <1% of all thyroid tumors.<sup>1</sup> Current literature reports that most thyroid collision tumors (TCT) are due to the co-occurrence of papillary (PTC) and medullary thyroid carcinomas (MTC).<sup>2</sup> However, there are only 20 cases to date that describe the concurrent presentation of both PTC and follicular thyroid carcinoma (FTC).<sup>3–18</sup>

## 2 | CASE PRESENTATION

A 58-year-old woman presented to a family medicine clinic for a routine check-up. An asymptomatic 1.5 cm; mobile, thyroid nodule was palpated on a routine physical exam. Her past medical history was positive for GERD

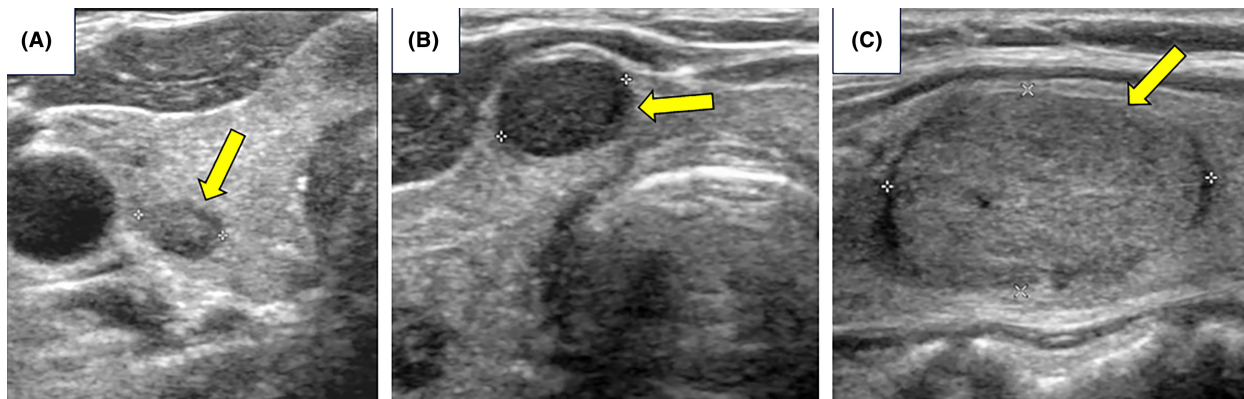
and seasonal allergies, controlled with pantoprazole, fluticasone, and cetirizine. She denied a history of smoking, recreational drug use, or alcohol consumption. The patient had no history of radiation to the head and neck, and no family history of endocrinopathies, thyroid, parathyroid, or pancreatic cancers.

### 2.1 | Investigation

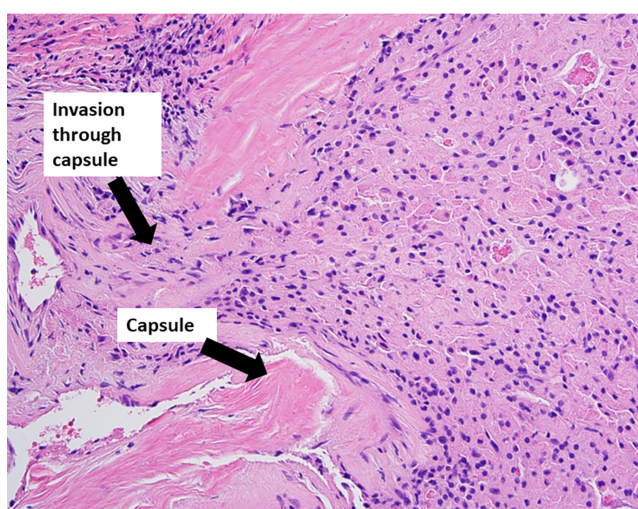
Her thyroid function tests were TSH 1.02 mIU/L (normal 0.3–4) and free T4 17.11 pmol/L (normal 9–23). Neck ultrasound was interpreted using the American College of Radiology's thyroid imaging, reporting, and data system (TI-RADS). The patient's neck ultrasound showed a 0.6×0.4×0.6 cm hypoechoic nodule without microcalcifications in the inferior pole of the right lobe (TI-RADS 2; [Figure 1A](#)), a 0.7×0.7×0.5 cm hypoechoic nodule of the right lateral isthmus (TI-RADS 2; [Figure 1B](#)), and a

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**FIGURE 1** Representative thyroid ultrasound images: These figures illustrate the representative thyroid ultrasound images taken in the transverse plane of the (A) lower pole of right thyroid lobe (B) right lateral isthmus and (C) superior pole of the left thyroid lobe. Yellow arrows point to the suspicious lesions in question.



**FIGURE 2** H&E stain of follicular thyroid carcinoma: This figure demonstrates the follicular thyroid carcinoma composed of oxyphil cells invading in an advancing V-shape through the thick fibrous capsule.

2×1.2×1.7 cm isoechoic, solid nodule without microcalcifications in the superior pole of the left lobe (TI-RADS 3; [Figure 1C](#)). Fine needle aspiration (FNA) biopsy of the left thyroid nodule showed a follicular neoplasm composed of follicular and Hürthle cells (HC), categorized as Bethesda IV.

## 2.2 | Treatment

The patient was qualified for a left-sided thyroid lobectomy. Upon surgical dissection of the neck, there was no lymphadenopathy or evidence of gross extra-thyroidal extension. Pathology showed a stage I (T1, N0, M0), 0.6 cm FTC, HC variant with focal vascular invasion in the lateral isthmus of the right lobe ([Figure 2](#)), a 1.8 cm classic PTC,

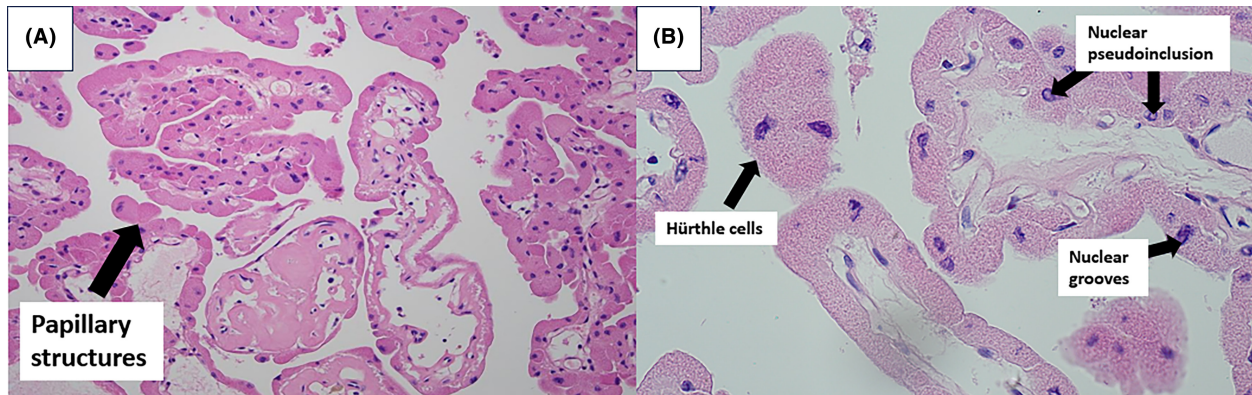
oxyphilic variant, with lympho-vascular invasion and HCs in the superior pole of the left lobe ([Figure 3A,B](#)), and a 0.6 cm papillary microcarcinoma, oxyphilic variant, in the inferior pole of the right lobe. Based on the high-risk nature of the lesions in both lobes, the patient underwent a total thyroidectomy. Central neck lymph nodes (Level VI) anterior to the trachea were dissected and sent for pathology. Surgical margins were clear, and none of the eight lymph nodes taken at the time of surgery demonstrated evidence of disease. The patient was immediately started on 137 mcg levothyroxine suppressive treatment with a goal TSH of 0.1–0.5 mIU/mL following the thyroidectomy. A month after surgery, radioactive iodine (RAI) uptake scan demonstrated minimal residual thyroid tissue with no abnormal localizations to suggest distant metastasis ([Figure 4A,B](#)). Given the presence of lympho-vascular invasion and HC histology, the patient underwent RAI ablation with 153.9 mCi of I-131 a month after surgery.

## 2.3 | Outcome and follow up

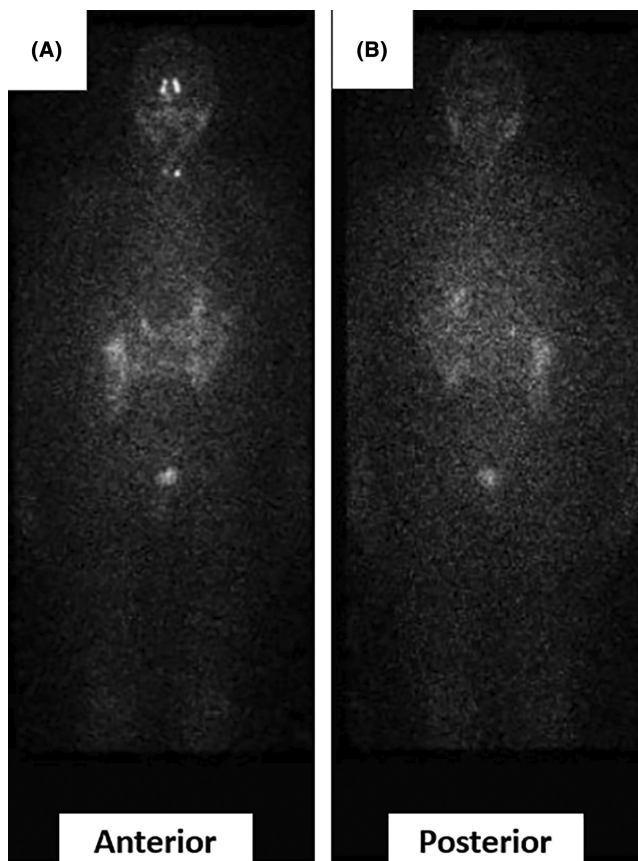
Following thyroidectomy, subsequent follow-up over the next 7 years with annual surveillance neck ultrasounds have been unremarkable. Similarly, unstimulated thyroglobulin, and anti-thyroglobulin antibody drawn 9 months after ablation, and annually afterwards have been normal, suggesting that there is no structural or biochemical recurrence of disease.

## 3 | DISCUSSION

PTC and FTC are both derived from thyroid follicular cells. Of the two, PTC is the most common thyroid malignancy, accounting for 70%–90% of all differentiated thyroid cancers.<sup>2</sup> FTC is the second most common differentiated



**FIGURE 3** H&E stain of (A) papillary thyroid carcinoma: The tumor is composed of separated fibrovascular cores covered by epithelial cells with rich oxyphilic cytoplasm. (B) Hürthle cells: 400 $\times$  of the papillary thyroid carcinoma illustrating Hürthle cells with their finely granular, eosinophilic cytoplasm with round and oval nuclei with prominent nucleoli. Other common characteristics of papillary thyroid carcinoma are illustrated including nuclear pseudo-inclusions and nuclear grooves.



**FIGURE 4** Postoperative I-123 thyroid uptake scan. (A) Anterior and (B) posterior views. Images show expected post-surgical radioactive iodine distribution. Minimal residual thyroid tissue is identified with no abnormal localizations to suggest distant metastasis. Total thyroid bed uptake was 0.36%.

thyroid cancer, accounting for 10%–15% of cases.<sup>2</sup> Thyroid cancers can also occur simultaneously, a phenomenon known as “thyroid collision tumours.” TCTs are rare and account for less than 1% of all thyroid tumors.<sup>1</sup> TCTs are

two histologically distinct tumors found in the same organ and separated by normal tissue.<sup>1</sup> Tumors can be of thyroid origin or from metastatic sites. The most reported TCT is PTC and MTC as highlighted in a recent case series by Ryan et al.<sup>2</sup> Though the co-occurrence of PTC and other carcinomas in the thyroid have been reported,<sup>19</sup> the co-existence of PTC and FTC are extremely rare, with only 20 cases reported in the English literature.<sup>3–18</sup> Among the cases of co-existent PTC and FTC, the median age is 56 years old (range: 12–79 years old), with a female preponderance (66%) as per our review of current published English literature. Additionally, lymph node metastasis was reported in four patients,<sup>5,6,13,15</sup> and distant metastasis to the rib/femur/shoulder bone, and adrenal gland have also been reported in four patients.<sup>5,6,9,11</sup> TCTs seemed to be located mainly either in the right lobe ( $n=8$ ),<sup>3,10,13–15</sup> or both lobes ( $n=10$ ),<sup>5–9,11,12,17,18</sup> as opposed to only in the left lobe ( $n=3$ ).<sup>3,16</sup> Lastly, only 6 of 20 patients had TCTs with 2+ foci.<sup>3,12,14</sup> Our case of TCT in a 58-year-old woman with a TCT of 2+ foci located in both lobes with no lymph node or distant metastasis represents one of the rarer tumors currently represented in the PTC/FTC TCT literature.

Multiple techniques were used to diagnose TCT in our case including neck ultrasound, FNA biopsy with cytopathology, and surgical pathology. Ultrasonography of the thyroid using the TI-RADs grading scale is both sensitive and specific to further guide the investigation of asymptomatic thyroid nodules.<sup>20</sup> TI-RADs risk stratifies patients using a standardized scoring<sup>1–5</sup> system determined from five categories of ultrasound findings (composition, echogenicity, shape, margin, and echogenic foci). Higher cumulative scores indicate a greater likelihood of malignancy.<sup>21</sup> Cytopathology of FNA biopsies rarely detects two distinct tumors such as in TCTs. Furthermore, cytologic analysis of FTC can be

challenging as diagnostic hallmarks of follicular carcinoma (e.g. angioinvasion or capsular invasion) cannot be detected by cytology alone.<sup>22</sup> However, FNA can identify malignant pathologies.<sup>2</sup> Further characterization via immunohistochemistry allows for delineation of two separate tumors. Additionally, immunohistochemistry and molecular testing can be important in informing the prognosis. For example, BRAF V600E mutations are the most frequently detected genetic mutations in PTC and are found in 35–80% of adults carrying these cancers.<sup>23</sup> PTC positive for BRAF mutations and TERT promoter mutations reportedly have higher frequencies of lymph node metastasis, tumor recurrence, and extra-thyroidal extension portending a poorer prognosis in affected patients.<sup>23,24</sup> However, given the high prevalence of BRAF V600E, it is not practical to recommend aggressive treatment for PTC based on BRAF status alone. Liu et al. suggest an intriguing mortality risk stratification system using a “genetic duet” of BRAF V600E and TERT promoter mutations in PTC, however further studies are needed to clarify the clinical utility of using molecular analysis on clinical decision making, especially in TCTs.<sup>24</sup> Indeed, a handful of cases of PTC/FTC TCTs have reported genetic alterations in BRAF and TERT promoter in PTC and, NRAS mutations in FTC. However, among these limited number of cases, there is an unclear association between aggressiveness of disease and molecular phenotype.<sup>6,13,15</sup> Unfortunately, neither immunohistochemistry nor molecular testing was done in our case. For suspicious lesions, cytology of FNA biopsy is a good first step, however, surgical pathology remains the most reliable diagnostic tool in characterizing TCTs.

Treatment of TCTs poses a special challenge as they contain elements with different aggressiveness, treatments, and prognoses. Some experts suggest that in the case of multiple tumors, the most aggressive tumor should define the treatment.<sup>2</sup> Others contend that each component of the TCT should be treated as a separate primary entity.<sup>14</sup> Nevertheless, the decisions on treatment should be made on a case-by-case basis based on biological aggressiveness, stage of the tumor, and patient preferences.<sup>2</sup> There are no evidence-based guidelines regarding the treatment of TCTs; however, we treated our patient based on the most aggressive cancer. A few cases have shown that total thyroidectomy seems to have favorable clinical outcomes in co-existent PTC and FTC.<sup>8,10,11</sup> Additionally, our patient was treated with adjuvant RAI ablation following thyroidectomy. Based on the 2023 National Comprehensive Care Network guidelines, RAI should be recommended if a PTC has any of the following features: significant N1b disease, gross extra-thyroidal extension, primary tumor >4 cm,

bulky/>5 positive lymph nodes, and/or vascular invasion.<sup>25</sup> Our patient's TCT had a PTC component that demonstrated lymphovascular invasion and concerning HC histology. Therefore, we opted to treat the patient's TCT with adjuvant RAI ablation. Lastly, the patient continues to receive levothyroxine suppressive therapy that was initially started at 137 mcg directly after thyroidectomy and titrated down to 88 mcg after 36 months. This was because the patient's levothyroxine was started with a goal TSH of 0.1–0.5 mIU/mL after thyroidectomy given an intermediate risk of recurrence. The goal was relaxed to 0.5–2 mIU/mL 3 years after thyroidectomy. Evidence supporting TSH suppression is strongest in cases of differentiated thyroid cancers, such as in patients with TCT.<sup>26</sup> Several studies demonstrated that normal-high serum TSH was associated with a higher frequency of differentiated thyroid cancer in patients with thyroid nodules, as well as a more aggressive course in patients with thyroid cancer.<sup>26</sup> Current American Thyroid Association guidelines recommend a graded approach to TSH suppression based on initial risk and ongoing risk assessment.<sup>27</sup> Overall, the patient's TCT had an excellent treatment response with no disease recurrence to date.

Regarding the histopathology of thyroid cancer in this case, the presence of HCs (also known as oncocytic, oxyphilic, or Askenazi cells) may be of prognostic significance. HCs originate from follicular cells and are characterized by eosinophilic cytoplasm with round or oval nuclei, prominent nucleoli, and densely packed mitochondria.<sup>28</sup> Importantly, HCs may be present in non-neoplastic (i.e., toxic goiter, Graves disease, Hashimoto's thyroiditis) and neoplastic conditions. Hürthle cell carcinomas (HCCs) are diagnosed when more than 75% of the tumor consists of HCs.<sup>29</sup> HCCs are more aggressive than PTC or FTCs, carry a worse prognosis, and respond poorly to RAI treatment.<sup>28</sup> Therefore, HCCs have been named as a distinct neoplastic entity by the 2017 World Health Organization guidelines on Pathologic Classification of Thyroid Neoplasms.<sup>29</sup> The prognosis of PTCs with HCs does not seem to be significantly different than their non-HC-containing counterparts.<sup>30</sup> Herrera et al. analyzed 22 cases of oxyphilic PTC and compared them with differentiated PTC and oxyphilic FTC. After 10 years post-resection, the tumor recurrence and cause-specific mortality rates of oxyphilic FTC were 28% and 18%, insignificantly different from 28% and 17% seen with the oxyphilic PTC.<sup>31</sup> However, the study was most likely grouping FTC and HCC together, rather than analyzing FTC with HCs as a separate entity. To date, no studies have investigated the prognosis of FTCs and HC-containing FTCs in the setting of the newest WHO classification scheme for HCC. Future work must clarify

the prognosis of HCs in FTC and PTC and whether the mere presence of HCs has a prognostic significance. In our case, though there were HCs present in the FNA and surgical pathology, the combined picture of relatively high tumor burden and presence of lympho-vascular invasion led us to proceed with thyroidectomy followed by adjuvant radioiodine ablation of thyroid tissue remnants.

With regards to prognosis, some suggest that TCTs are more aggressive than singleton tumors<sup>32</sup>; however, Ryan et al. reported in a case series of 33 patients that TCTs and singleton tumors exhibited near equal aggressiveness lending to a similar prognosis as those with singleton pathology.<sup>2</sup> This is corroborated by other authors who report that metastatic and survival rates in co-existent PTC and FTC are consistent with matched singleton pathology.<sup>10</sup> In our patient, the thyroid nodule was diagnosed early, and subsequent investigation and follow-up were not delayed leading to a favorable outcome 7 years after treatment.

## 4 | CONCLUSION

Overall, PTC and FTC collision lesions are extremely rare but are being increasingly reported. Thus, this case highlights an important clinical entity that clinicians must be cognizant of. To date, there is no consensus regarding the diagnosis and treatment of PTC and FTC collision tumors given their rarity. Much of the existing literature has lacked data on the molecular characterization of these tumors and long-term follow-up in patients with PTC and FTCs. Reporting of this data will be valuable in informing standardized diagnostic and treatment protocols.

### AUTHOR CONTRIBUTIONS

**Vijayvardhan Kamalumpundi:** Data curation; formal analysis; investigation; visualization; writing – original draft; writing – review and editing. **Erin Meyers:** Data curation; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Maisoon Torfah:** Conceptualization; investigation; methodology; project administration; supervision; validation; visualization; writing – review and editing. **Marcelo Lima de Gusmão Correia:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing.

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### CONFLICT OF INTEREST STATEMENT

The four authors listed above have no conflicts of interest to declare that are relevant to the published work.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

### CONSENT


Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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