Endocrinology, Diabetes & Metabolism CASE REPORTS

S J Kim and others | FTC mimicking pulmonary adenocarcinoma

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Recurrent follicular thyroid carcinoma metastatic to axillary lymph nodes mimicking pulmonary adenocarcinoma

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Abstract

Differentiated thyroid cancers generally have favorable prognoses, though follicular thyroid cancer is overall associated with a worse prognosis due in part to increased incidence of distant metastasis. We report a case of a 51-year-old woman with a history of widely invasive follicular thyroid carcinoma treated with a total thyroidectomy, radioactive iodine and external beam radiation. Five and a half years following her surgery, she was found to have an axillary lymph node mass, multiple lung masses, and a hilar mass in the setting of declining thyroglobulin (Tg) antibodies. Her metastases were initially thought to be due to a primary lung adenocarcinoma given a neoplastic cell immunophenotype that included an absence of Tg expression and co-expression of TTF-1 and Napsin A. However, PAX8 expression demonstrated that the axillary and hilar metastases were actually thyroid in origin rather than lung. Axillary metastases in differentiated thyroid carcinoma are exceedingly rare and previous reports have typically involved widely disseminated disease with extensive neck lymphadenopathy. With a decline in Tg antibodies levels in high-risk patients, one should consider progression and loss of differentiation of thyroid carcinoma rather than a response to treatment.

Learning points:

- Axillary metastases in differentiated thyroid carcinoma are uncommon.
- In patients with high-risk thyroid carcinomas, a decline in thyroglobulin antibody may not signal disease improvement, but rather a progression to a poorly differentiated form of cancer.
- PAX8 staining can be used to differentiate thyroid carcinomas from lung adenocarcinomas.

Background

Differentiated thyroid cancers, including follicular thyroid carcinoma (FTC) and papillary thyroid carcinoma (PTC), are generally associated with favorable prognoses (1). FTC is the second most common differentiated thyroid cancer, historically accounting for up to 10–15% of all thyroid malignancies (2). Distant metastases, most commonly lung and bone (3) are found at presentation in up to 27% of FTCs (4) and up to 46% of patients with extensive vascular invasion on histology (3). Compared to PTC, FTC is overall associated with a worse prognosis due in part to this increased presence of metastases.

Cervical lymph node metastases are less common in FTC with an incidence of 2–8% increasing to 17% in invasive disease (2, 5). This is compared to an incidence of up to 50% for PTC (6). Axillary lymph node metastases have previously been described in only eight patients with

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PTC (7) and only one patient with FTC (8). Here, we report a second case of late axillary lymph node metastasis in a patient with invasive FTC that was initially misdiagnosed as metastatic pulmonary adenocarcinoma.

Case presentation

A 51-year-old woman originally presented with a 1-year history of an asymptomatic enlarging neck mass. CT revealed a 10 × 5 × 6 cm left thyroid mass with invasion into the left internal jugular (IJ) and brachiocephalic veins. A fineneedle aspiration of the mass was consistent with a follicular neoplasm. Immunohistochemical (IHC) staining was positive for thyroglobulin (Tg) with weak, patchy staining for both thyroid transcription factor-1 (TTF-1) and p53. Staining was negative for calcitonin, excluding medullary thyroid cancer. While lymph node mapping was not performed at that time, further imaging with MRI confirmed vascular invasion into and occlusion of the left jugular and brachiocephalic veins.

Investigation

The patient underwent total thyroidectomy and central neck and mediastinal dissection with *en bloc* resection of the left internal jugular and brachiocephalic veins. Tumor was grossly adherent to the trachea, adherent to the strap muscles, and invading the recurrent laryngeal nerve. Pathology showed an 8.9 cm FTC with extensive invasion into multiple vessels and extrathyroidal extension into skeletal muscle. The left internal jugular vein was occluded with tumor thrombus which extended into the brachiocephalic vein. There were positive resection margins superior to the left internal jugular vein, and on the right margin of the left brachiocephalic vein. Three level VI nodes were removed and all were negative for tumor. Routine histologic sections showed the neoplastic follicular cells were arranged in a microfollicular pattern. In other areas, the tumor showed solid growth, frequent mitoses, and tumor necrosis (Fig. 1). The tumor was staged as pT4N0M0. Approximately 1 month postoperatively, laboratory testing showed a Tg of 0.1 ng/mL (reference range: 1.3–31.8 ng/mL) and anti-thyroglobulin antibody (anti-Tg ab) of 561 IU/mL (0–14.4 IU/mL).

Treatment

The patient was treated with 150 mCI of I-131. Pretreatment whole-body scan (WBS) showed 2.9% uptake at 24 h, all in the thyroid bed. Post-treatment WBS again showed uptake confined to the thyroid bed. At the time of treatment, Tg was detectable at 0.5 ng/mL with a TSH of 167 mIU/mL and anti-Tg ab of 425.5 IU/mL. Given the degree of extrathyroidal extension, she received external beam radiation to the neck and thyroid bed. Neck ultrasound and MRI 10 months following her initial surgery showed no evidence of recurrence and anti-Tg ab, while still present, were declining (Fig. 2). Diagnostic I-131 WBS at 1.5 years revealed only physiological uptake in the right submandibular gland. TSH stimulated Tg was < 0.1 ng/mL, and she received no further treatment. Anti-Tg ab remained detectable. Two and a half years following

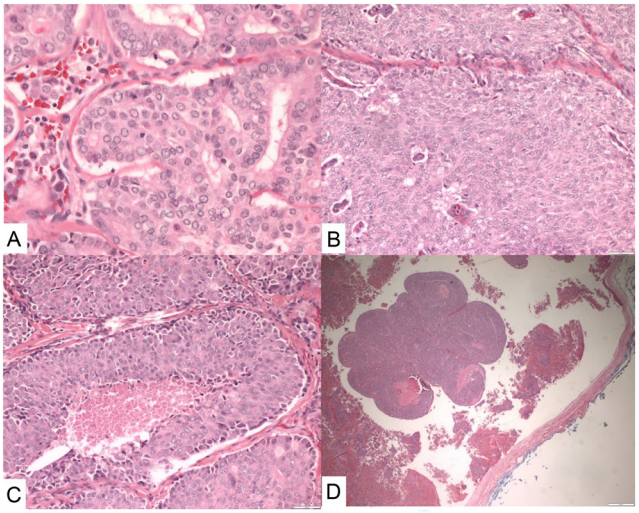

Figure 1
Neoplastic cell growth patterns and morphology in thyroidectomy specimen. Routine sections from thyroidectomy show neoplastic follicular cells with a predominately microfollicular growth pattern (A). No features of papillary thyroid carcinoma are seen. Other areas of the neoplasm show solid, sheet-like growth without follicle formation (B) and tumor necrosis (C). The internal jugular vein margin was grossly involved by neoplasm and shows an intraluminal thyroid carcinoma admixed with blood clot (D). Hematoxylin and eosin, original magnification, ×400 (A), ×200 (B, C), ×20 (D).

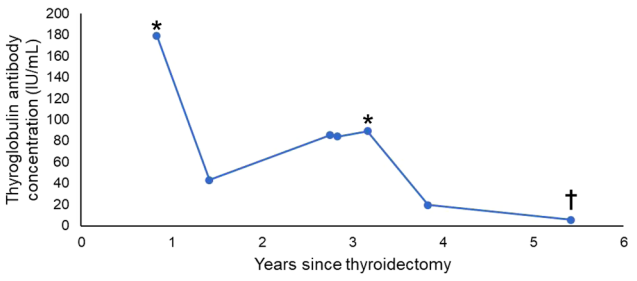

Figure 2
Trends in anti-thyroglobulin antibody (anti-Tg Ab) concentration (reference range: 0–4.0 IU/mL) over time. *I-131 treatment; † Diagnosed with metastatic FTC.

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surgery, in the setting of the continued presence of and rising anti-Tg ab accompanied by a minimal increase in TSH stimulated Tg from <0.1 to 0.2 ng/mL, she received an additional 150 mCi of I-131 therapy due to the concern for persistent disease. Post-treatment WBS showed no uptake. While anti-Tg abs remained detectable, they did decline post-treatment (Fig. 2) and neck imaging continued to reveal no residual tissue. Subsequent to her second I-131 treatment, measures of Tg in the setting of positive anti-Tg Ab were performed using LC-MS/MS. Initial testing with that method revealed an undetectable TSH-suppressed Tg. One year later she TSH-suppressed Tg was detectable at 1.6 ng/mL in the setting of a significant decline in anti-Tg Abs; however, the next Tg was again undetectable and anti-Tg Ab further decreased to 5.4 IU/ml at that time.

Outcome and follow up

Five and a half years following surgery, the patient presented with a 3-day history of a non-productive cough, fever, chills, and tachycardia. A chest CT (CT) scan obtained to assess for pulmonary embolism showed a 2.7 cm right hilar mass and 1.8 cm irregular spiculated solitary pulmonary nodule in right lower lobe, suspicious for pulmonary malignancy. No pulmonary embolism was found.

A fine-needle aspiration biopsy of the hilar lesion was performed and showed metastatic carcinoma expressing TTF-1 (Fig. 3, panel F) and Napsin A (Fig. 3, panel H) by IHC, which was initially considered diagnostic of pulmonary adenocarcinoma. She had no smoking history. Molecular testing for recurrent genetic abnormalities commonly found in pulmonary adenocarcinoma, including ALK fluorescence in situ hybridization, EGFR and BRAF pyrosequencing, and ROS1 IHC, did not show any alterations.

Staging PET-CT showed hypermetabolic left axillary lymph nodes that were subsequently sampled by ultrasound-guided fine-needle aspiration biopsy for lung adenocarcinoma staging. Sections of the axillary lymph node cell block showed a microfollicular arrangement of

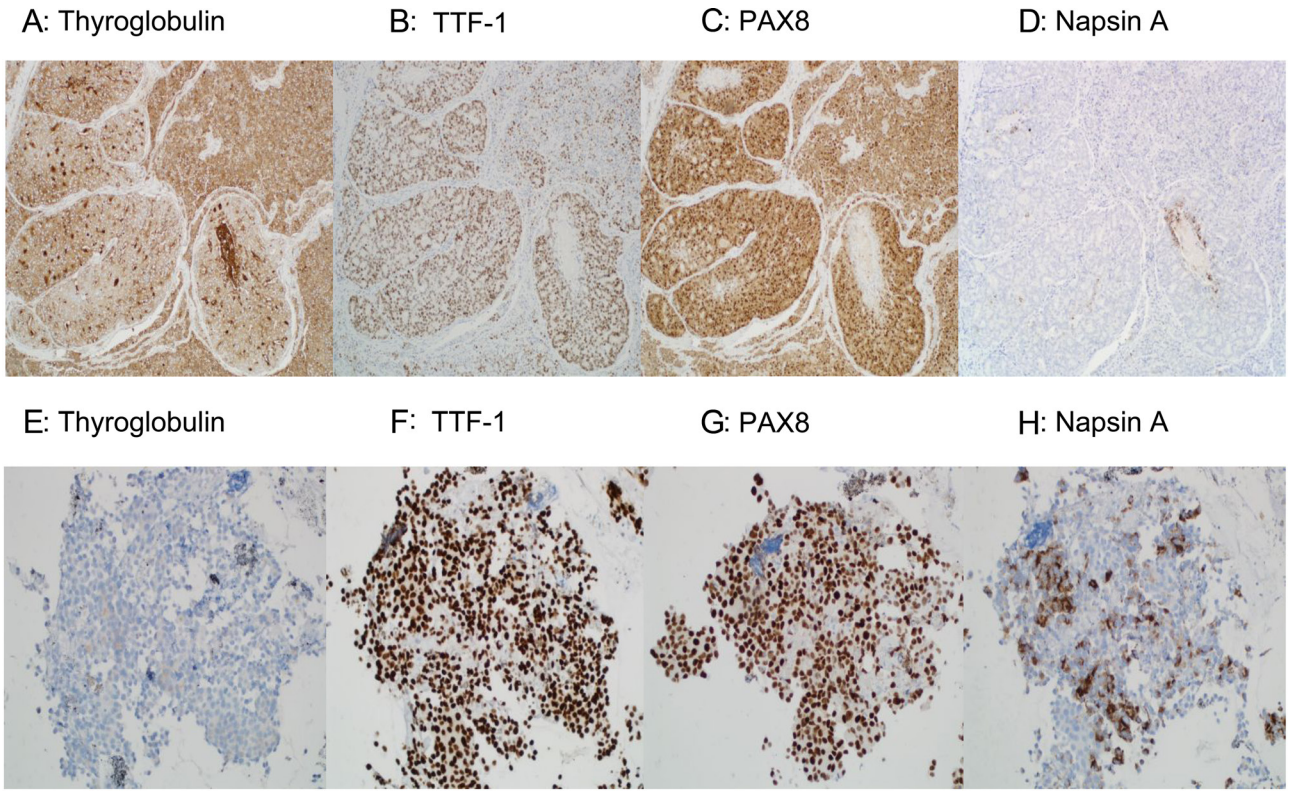

Figure 3
Immunoprofile comparison of primary and metastatic thyroid carcinoma. Immunohistochemical stains performed on the thyroidectomy specimen show the neoplastic cells express Tg (A), TTF-1 (B), and PAX8 (C), and lack Napsin A (D). However, immunostains performed on the hilar metastasis show neoplastic cells lack Tg (E) and express TTF-1 (F), PAX8 (G) and focal Napsin A (H). Tg, TTF-1, PAX8, Napsin A, original magnifications, ×100 (A, B, C, D), ×40 (E, F, G, H).

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neoplastic epithelial cells, suggesting thyroid origin. IHC performed on the axillary lymph node cell block showed that the neoplastic cells expressed TTF-1 and PAX8 but lacked Napsin A and Tg, an immunoprofile diagnostic of metastatic thyroid carcinoma. Subsequent IHC performed retrospectively on the hilar biopsy specimen showed the tumor expressed PAX8 and lacked Tg (Fig. 3, panels E, F, G and H). The original thyroidectomy specimen was also stained and demonstrated that the neoplastic cells expressed Tg, TTF-1, PAX8, and focal Napsin A (Fig. 3, panels A, B, C and D). Given the PAX8 expression, the hilar biopsy specimen diagnosis was revised from lung adenocarcinoma to metastatic FTC.

The expression of PAX8 but not Tg in both the hilar and axillary lymph node metastases, in conjunction with minimally elevated anti-Tg ab (5.7 IU/mL; ref 0–4.0 IU/mL) and an undetectable Tg (<0.5 ng/mL; ref 1.3–31.8 mg/mL), suggested a loss of differentiation in this formerly differentiated FTC. Therefore, she was treated with tyrosine kinase inhibitors (TKIs) rather than additional I-131. Unfortunately, her disease progressed rapidly, and she died 7 years after her initial diagnosis.

Discussion

Axillary lymph node metastasis in thyroid carcinomas is rare with only a handful of case reports in PTC (7, 9) only one prior case reported in FTC (8). The few reported cases of axillary metastases are generally observed in the setting of widely disseminated disease and can be a very late recurrence, as was the case with our patient who presented 5.5 years after her initial diagnosis.

Cervical lymph node metastases are more commonly observed in PTC, while distant metastases to sites such as the lung or bone are more common with FTC due to hematogenous spread (4). Thus, a case of distant lymph node metastasis in FTC is highly unusual. The previous case of FTC metastatic to an axillary node was in a patient with widely disseminated disease who presented with a pathologic fracture, bone and liver metastases, and extensive cervical, supraclavicular and axillary lymph node metastases (8). Also, the pathology, in that case, was unusual with signet ring cells and suggested a dedifferentiated tumor, though it remained iodine avid. In our case, the tumor was poorly differentiated and not iodine avid. In addition, the patient had no other extensive cervical lymphadenopathy making the axillary metastasis even more unexpected. We hypothesize that the axillary lymph node metastasis resulted from residual tumor in the subclavian vein. The lymphatic and venous systems are closely aligned, and malignant tumors can alter and partially block lymphatic pathways, causing disease to spread in a retrograde direction along the transverse cervical lymph nodes in the supraclavicular region, which can cause axillary lymph node metastasis (7). All reported cases of axillary lymph node metastases have been associated with poorly differentiated thyroid carcinoma and may be an indicator of systemic disease and poor prognosis (9).

While more commonly see in lung adenocarcinoma, Napsin A expression can also be present in up to 7% of FTCs. Therefore, co-expression of TTF-1 and Napsin A is not entirely specific and should not be considered diagnostic of lung adenocarcinoma (10). Further confounding the overlapping immunophenotypes is that poorly differentiated areas of follicular thyroid carcinoma, as in our case, can lack thyroid-specific markers like Tg both by tissue immunostaining and serum. In these cases, PAX8 expression can be used to differentiate between a thyroid carcinoma and a lung adenocarcinoma, and one should have a low threshold to order this marker in any patient with a history of a primary thyroid malignancy.

In retrospect, our patient's disease was RAI-refractory and the uptake in her central neck with her initial treatment was likely residual thyroid rather than cancer. In this setting, newer research suggests she may have benefitted from TKI therapy with a MEK inhibitor prior to subsequent retreatment to induce iodine uptake and retention in the cancer cells (11). Additionally, incorporating an assessment of the axillary region on examination, given the increased potential for malignant spread to this location, may have led to earlier detection of her recurrent disease. Finally, a PET-CT at the time of the detectable Tg using LC-MS/MS would likely have revealed her metastatic disease. Subsequent disappearance of Tg was likely indicative of tumor dedifferentiation rather than the absence of disease.

In conclusion, we report a case of dedifferentiated FTC metastasizing to the axillary lymph nodes. Our case highlights that, in some patients with high-risk thyroid carcinomas, a decline in anti-Tg ab may not signal disease improvement, but rather a progression to a poorly differentiated form of cancer that ultimately carries a worse prognosis. Additionally, PAX8 staining can be used to differentiate thyroid carcinomas and lung adenocarcinomas, as axillary lymph node metastasis and overlapping immunophenotypes can present in both.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
The patient is deceased and the patient's relative cannot be traced. The authors have made all attempts to anonymize the patient.

Author contribution statement
S J K wrote the first draft of the manuscript, contributed to interpretation of the data, made critical revisions for intellectual content, and approval the final version of the manuscript. E M B, M R, J M, and E J M contributed to the interpretation of the data, made critical revisions for intellectual content, and approved the final version of the manuscript.

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