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Case Report

Hidden in Plain Sight: Incidental Diagnosis of Metastatic Papillary Thyroid Microcarcinoma Without Radiologically Apparent Thyroid Tumor

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ABSTRACT

Background/Objective: Papillary thyroid cancer (PTC) is considered the most common form of thyroid cancer. Papillary thyroid microcarcinomas (PTMCs) are defined as papillary carcinomas that are <1 cm and are often identified on surgical pathology but may be missed by ultrasound imaging.
Case Report: Our case describes a 24-year-old woman who initially presented with a right lateral neck lump. This was thought to be a lipoma, and no workup was performed until it began to grow during pregnancy 3 to 4 years after initial presentation. The patient underwent excision with findings of a level 5B lymph node with pathology consistent with PTC, follicular variant. Neck ultrasound performed in an imaging center and in our clinic did not reveal thyroid nodules or abnormal appearing lymph nodes. Solid tumor profiling assay identified a neurotrophic tropomyosin receptor kinase (NTRK)-3 fusion: ETV6(4)-NTRK3(14) mutation.
Discussion: PTMCs are identified with increased frequency due to improved ultrasound imaging and fine needle aspiration techniques. PTMCs are often associated with a benign course and are rarely metastatic. There has been growing interest in NTRK fusion mutations in PTC that has been associated with an increased risk of metastasis.
Conclusion: This case is unusual in that multiple cervical nodal metastases were present even without a sizable primary thyroid tumor. Although more studies are needed to elucidate the clinical and prognostic significance of NTRK fusion mutations in PTMC, their response to tropomyosin receptor kinase inhibitors may represent a future pathway for treatment.

Introduction

Papillary thyroid cancer (PTC) is considered the most common form of thyroid cancer. Although PTC commonly spreads to nearby lymph nodes, it typically carries a favorable prognosis. However, various clinicopathologic and background characteristics indicate a poor prognosis. These features include older age, distant metastasis, lymph node metastasis, extrathyroidal extension, and tumor size and stage.[1] Papillary thyroid microcarcinoma (PTMC) is a specific subgroup of PTC with the largest dimension of ≤1.0 cm. Most of PTMCs are not detectable during clinical examination and are diagnosed incidentally during pathologic examination of thyroid specimens after surgery for benign thyroid diseases. In some cases, they are also identified with ultrasound but frequently missed, similar to our case. The incidence rate of thyroid cancer has been increasing all over the world. This increase could be attributed to advancement of diagnostic techniques.[1]

The prognosis of the disease is correlated with different mutations occurring in thyroid cancer. The BRAF V600E mutation is the most frequently observed mutation, and it has been linked to an

Abbreviations: HCA, Hospital Corporation of America; NTRK, neurotrophic tropomyosin receptor kinase; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma; TRK, tropomyosin receptor kinase.

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increased risk of cancer recurrence. Nevertheless, recent meta-analyses have challenged this association.[2] Other genetic alterations that have significant prognostic and therapeutic implication in PTC rearrangements include the neurotrophic tropomyosin receptor kinase (NTRK).[3] Determination of NTRK activation status has recently gained high clinical utility since the emergence of targeted inhibitor therapy.

Here, we describe a case of a patient diagnosed with metastatic PTMC without apparent thyroid tumor on imaging.

Case Report

We present the case of a 24-year-old woman who initially presented with a right lateral neck lump. This was present for 3 to 4 years, and she was told that this was likely a lipoma. Therefore, no workup was performed until it began to grow during pregnancy. After delivery, she had neck ultrasound, which showed a right level 5B mass that was believed to be a lipoma (Fig. 1).

Following pregnancy, she underwent excision with findings of a level 5B lymph node measuring 2.1 × 2.1 × 0.9 cm with pathology consisting of PTC, follicular variant (Fig. 2). Neck ultrasound performed in an imaging center and in our clinic did not reveal thyroid nodules or abnormal appearing lymph nodes. She was referred for total thyroidectomy with central neck and limited right neck dissection. Surgical pathology showed a 0.5-cm right superior lobe PTMC, follicular variant with negative surgical margins. Seven of 24 lymph nodes were positive in the right central compartment and in levels 3 and 4. The largest metastatic lesion measured 0.9 cm. Solid tumor profiling assay identified a NTRK3 fusion: ETV6(4)-NTRK3(14) mutation. She did well following surgery and had RAI ablation following thyroid hormone withdrawal. Two years later, a whole-body scan and neck ultrasound showed no signs of structural recurrence, and the thyroglobulin levels had remained undetectable. She had an excellent response to therapy with no recurrence to date. She is currently on 150 mcg of levothyroxine with thyroid-stimulating hormone at target goal of 0.1 mIU/mL and is doing well clinically.

Discussion

This case highlights several important aspects of PTMC, particularly the challenges in detection and management, as well as the potential role of molecular profiling in guiding treatment decisions.

Highlights

- Although papillary thyroid microcarcinoma often has a favorable prognosis, some highlight the necessity for meticulous assessment and aggressive treatment strategies
- Genetic profiling of thyroid tumors can provide insight into prognosis and help develop future therapeutics
- The identification of neurotrophic tropomyosin receptor kinase (TRK) fusion mutations opens new treatment pathways showing promising responses

Clinical Relevance

This case highlights the challenges in detecting and managing papillary thyroid microcarcinomas (PTMCs). It underscores the importance of thorough evaluation and molecular profiling in guiding treatment decisions. Additionally, it highlights the potential of tropomyosin receptor kinase inhibitors as a future therapeutic pathway for patients with PTMCs.

PTMCs are identified with increased frequency due to improved ultrasound imaging and fine needle aspiration techniques and may represent over 40% of PTC. Occasionally, these tumors are discovered during the histopathologic analysis of thyroid glands removed during surgery for conditions unrelated to thyroid malignancies or noncancerous thyroid disease.[1] A papillary microcarcinoma may occasionally be the primary lesion of a lymph node metastasis presenting clinically as a neck mass, similar to the patient in our case report, who initially presented with a neck nodule concerning for a lipoma that ended up being PTMC after complete thyroidectomy analysis. Verge et al[4] describe 7 cases in which cervical lymph node metastases were the initial and sole manifestation of PTC. In all cases, thyroid tumors were not palpable on physical examination, and no abnormalities of the thyroid gland were detected by other diagnostic procedures. A separate case by Schwaiger et al[5] describes a 40-year-old man with a slow-growing neck mass that was initially noted 9 years before presentation. The underlying cause turned out to be an occult PTMC measuring 6 mm, with metastatic invasion and subsequent cystic degeneration of cervical lymph nodes. Diagnosis was made following surgical intervention and histopathologic analyses.

PTMCs are generally considered to carry a favorable prognosis. However, PTMC sometimes exhibits aggressive behavior presenting

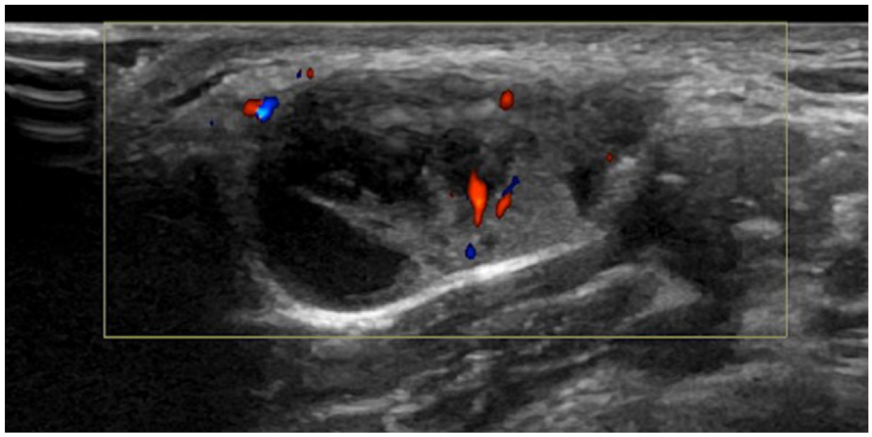

Fig. 1. Ultrasound of lateral V right neck mass (transverse view).

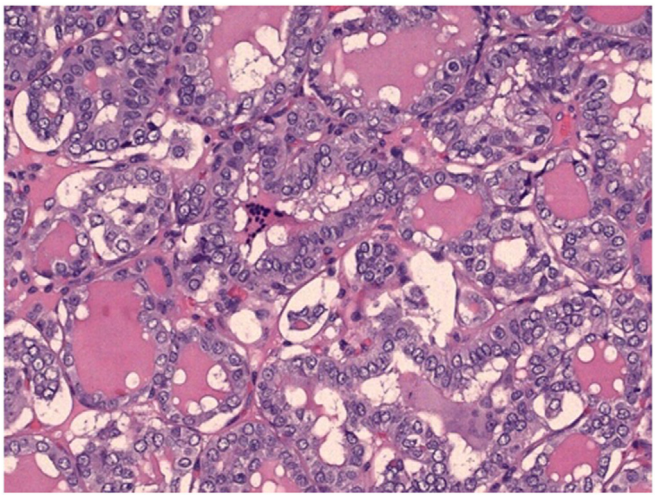

Fig. 2. Lymph node replaced by metastatic carcinoma.

with lymph node metastasis and local recurrence. The incidence of cervical lymph node metastasis varies widely in the literature but is reported in approximately 29% to 65% of patients with PTMC undergoing total thyroidectomy.[6] Node metastasis is also the main predictive factor for local recurrence. Multiple studies have shown that the size of the tumor is an independent factor for tumor metastasis. Specifically, a retrospective analysis on 293 cases found an incidence of lymph node metastasis of 6.3% in patients with tumors with size up to 5 mm and of 20.6% in patients with larger tumors.[7] This case is unusual in that nodal metastasis was present even without a sizable primary thyroid tumor seen on ultrasound imaging performed multiple times at different facilities.

Molecular analysis for genetic alterations in thyroid carcinoma can help with diagnosis, need of surgery and extent of it, and estimate prognosis. There has been growing interest in NTRK fusion mutations in PTC.[3,8] NTRK mutations have been previously described with higher frequency in pediatric populations but are increasingly recognized in adult cohorts.[3] NTRK fusion mutations are identified in up to 13% of PTMC, and some studies suggest a higher risk of metastasis.[3]

Both NTRK1 and NTRK3 are of interest in thyroid carcinomas given emergent potential of treatment because they are therapeutically targetable and sensitive to tropomyosin receptor kinase (TRK) inhibitors such as larotrectinib or entrectinib.[3,8] NTRK3 is usually fused with ETV6 in thyroid cancer, similar to that observed in our patient. There have been approximately 11 case reports of primary thyroid secretory carcinomas with ETV6-NTRK3 fusions, exhibiting a similar immunophenotype of secretory carcinomas of the breast and salivary glands.[8] Both NTRK-rearranged PTC and primary thyroid secretory carcinomas have been linked to aggressive clinical behavior in limited group studies and individual cases.[9] However, the existing literature remains scant and requires further substantiation.

Although more studies are needed to elucidate the clinical and prognostic significance of NTRK fusion mutations in PTMC, their response to TRK inhibitors may represent a future pathway for treatment. Larotrectinib and entrectinib have already been approved by the Food and Drug Administration for both the pediatric and adult populations. A study published by Park et al[10] reports the outcomes of 4 patients with advanced thyroid cancer who had NTRK gene fusions and were treated with larotrectinib. Sustained radiographic improvement was observed, and these patients continued the medication. In this study, entrectinib was also analyzed, and it demonstrated a 55% overall response rate among patients with brain metastases.[10] A different study conducted by Waguespack et al[11] investigated the efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma, and it demonstrated that larotrectinib exhibited durable antitumor efficacy in both adult and pediatric patients with TRK fusion-positive thyroid cancer, showing sustained disease control with a 24-month progression-free survival rate of 69%.[11]

Genetic profiling of unusual cases of thyroid tumors can enrich our understanding of PTC, provide insight into prognosis, and help develop future therapeutics. Further studies could question the definition of PTMC aiming to establish a revised threshold that enhances the differentiation between tumors exhibiting aggressive behavior, potentially necessitating aggressive surgery, and those displaying indolent characteristics. In addition, considering the promising results of TRK inhibitors in the treatment of PTC, more research is needed to focus on identifying resistance mechanisms to these medications, to extend effectiveness of treatment for prolonged periods.

Disclosure

The authors have no conflicts of interest to disclose.

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Statement of Patient Consent

Written informed consent for publication was obtained from the patient for publication of this case report and any accompanying images.

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