Rare distant metastases to pancreas, liver, and lung as initial presentation of mixed tall cell and columnar cell variants of papillary thyroid cancer

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Summary

The most common sites of distant metastases of papillary thyroid carcinoma (PTC) are lung and bone. Widespread distant metastases of PTC are rare and associated with poor overall prognosis. Metastases to sites such as liver and pancreas are extremely rare, and literature is sparse on overall survival. In this report, we present a 57-year-old man whose initial presentation of PTC was with pancreatic, liver, and lung metastases, and subsequently developed metastases to bone and brain. He underwent a total thyroidectomy, neck dissection, and tracheal resection. Pathology revealed a predominant columnar cell variant PTC with focal areas of tall cell variant, and genomic sequencing showed both PIK3CA and BRAF gene mutations. Radioactive iodine ablation with I-131 did not show any uptake in metastatic sites and he had progression of the metastases within 6 months. Therefore, therapy with lenvatinib was initiated for radioactive iodine refractory disease. Our patient has tolerated the lenvatinib well, and all his sites of metastases decreased in size. His liver and pancreatic lesions took longer to respond but showed response 6 months after initiation of lenvatinib, and he remains on full dose lenvatinib 18 months into treatment.

Learning points

- Papillary thyroid carcinoma (PTC) usually metastasizes to lung and bone but can rarely occur in many other sites.
- Patients with distant metastases have significantly worse long-term prognosis.
- Lenvatinib can be an effective treatment of radioactive iodine refractory PTC with rare sites of distant metastases.
- Lenvatinib can be an effective treatment of PTC with BRAF V600E and PIK3CA mutation.

Background

Papillary thyroid carcinoma (PTC) is common with an increasing incidence worldwide (1). While regional spread to neck lymph nodes is frequently present, distant metastases are uncommon (2). PTC is known to have a favorable long-term outcome with 10-year survival rates greater than 90% (3). However, when distant metastases occur, the prognosis becomes significantly worse with a 10-year survival of 42% (4). The most common sites of distant metastases are lung, bone, and less frequently, brain (5). Other sites have been rarely reported; pancreatic metastases are extremely rare (3). We present a case of a man whose initial presentation of PTC was with multiple organ metastases including pancreas, liver, and lung.
Case presentation

A 57-year-old man presented to his family physician with a 7-month history of progressive dyspnea on exertion. He was previously well and walking 5 km a day but was now getting dyspneic with 1 flight of stairs. He also noticed some new hoarseness in his voice.

He had a past medical history of depression, anxiety, and hypertension and was taking amlodipine. He had no family history of thyroid cancer and had no previous exposure to radiation. He had a 25 pack-year history of smoking and quit 5 years ago.

Investigation

Investigations for his respiratory symptoms included a chest X-ray, which showed patchy opacifications and a possible lung nodule. He was initially treated for pneumonia and a CT scan of the chest was done in follow-up. This showed multiple pulmonary nodules, a ring-enhancing liver lesion, and a large thyroid mass that was displacing the trachea. He was evaluated by an otolaryngologist and a fine needle aspiration of the thyroid mass showed numerous three-dimensional groups of large atypical epithelial cells with large oval nuclei and frequent nuclear inclusions consistent with PTC (Fig. 1). He proceeded to have a CT scan of his abdomen and pelvis, which revealed a 1.5 × 2.3 × 1.9 cm mass in the tail of the pancreas and fully elucidated the 6 × 6 × 5 cm liver lesion. Given the unusual sites of metastases, a liver biopsy was pursued and confirmed the diagnosis of metastatic PTC. Next-generation sequencing revealed both a BRAF V600E mutation and a PIK3CA mutation (T to A point mutation at nucleotide 1035 in exon 5 which results in the substitution of lysine for asparagine at amino acid 345).

Treatment

He underwent a total thyroidectomy, neck dissection, and tracheal resection. Pathology showed a 4.8 cm poorly circumscribed mass comprised of epithelial cells with nuclear features typical for PTC. The tumor was associated with fibrofatty soft tissue infiltration and extensive lymphatic channel and vascular invasion. Although areas of conventional papillary morphology were present, the predominant histological pattern was columnar cell variant, with nuclear pseudostratification, slight cytoplasmic clearing, and cytoplasmic vacuolization (Fig. 2). In addition, focal areas showed elongated cells with eosinophilic cytoplasm, in keeping with tall cell variant (Fig. 3).

The patient subsequently had radioactive iodine ablation with 200 mCi of I-131, and the follow-up whole body iodine scan showed uptake in the thyroid bed but no uptake in the metastatic sites. Within the subsequent 3 months, a follow-up CT scan showed progression of the lung metastases with development of bilateral pleural effusions as well as 2 new sites of metastases in the brain and bone. A 10 × 7 mm left frontal lobe and 3 mm occipital lobe brain metastases were treated with stereotactic radiation therapy. A bone scan also confirmed a new right manubrium bone metastasis. Given the progression of the...
disease, he was deemed radioactive iodine refractory (RAI-R) (6) and referred to medical oncology.

At this point, the decision was made to start therapy with lenvatinib 24 mg daily. He tolerated the treatment well at full dose and a repeat CT scan 3 months into treatment showed a significant decrease in the lung metastases and pleural effusions. He did not require any other therapeutic intervention for the pleural effusions. The liver lesion remained stable but less infiltrative with better-defined borders, and the pancreatic lesion was stable. Repeated CT scan at 6 months showed a further decrease in the lung and mediastinal metastases (Fig. 4), as well as decrease in the liver lesion from 5.5 × 4.7 cm to 4.6 × 4.1 cm (Fig 5).

**Outcome and follow-up**

At the most recent 18-month follow-up, the patient continued on full dose lenvatinib with no side effects affecting his quality of life. During his treatment course, he required one treatment interruption due to mild asymptomatic proteinuria which resolved after an angiotensin receptor blocker was initiated. The patient continues in a partial response and importantly there has been no progression in the central nervous system disease.

**Discussion**

Distant metastases in PTC occur in less than 10% of patients (6) and predominantly arise in the lung and bone (4). Many other sites of metastases have been reported, including the brain, liver, skin, salivary glands, eye, kidney, adrenal gland, gastrointestinal tract, and pancreas (3, 4, 7, 8) but are exceedingly rare, comprising less than 0.6% of the population (7). In a recent literature review (3), only 24 cases of pancreatic metastases from PTC have been reported. Pancreatic metastases are mostly confined to a single region of the pancreas and concurrent metastases to other sites (lung, liver, bones, and skeletal muscle) are often present (2, 3, 7, 9, 10).

Several histological variants of PTC, including diffuse sclerosing, tall cell, columnar cell, solid, and hobnob carry higher rates of recurrence and metastases, as well as lower survival rates (11). Columnar cell variant is a very rare subtype, accounting for 0.15–0.2% of all PTC, and is associated with rapid growth rate, local invasion, and early metastasis (12). Tall cell variant is the most common aggressive variant, present in ~2% of PTC (13). Tall cell variant PTC has increased prevalence in males and older age, and similar to columnar cell variants, also has increased local invasion and metastasis (13). Our patient had both columnar and tall cell variant, increasing the concern for poor prognosis. Only two reports have shown co-existing tall cell and columnar cell variants (14), both resulting in mortality from lung metastases.

Our patient also had interesting genetic sequencing, with both a *BRAF* 600E and a *PIK3CA* mutation. *BRAF* gene mutations are detected in 45–52% of cases of PTC (15, 16) and have association with more aggressive histologic phenotypes, increased risk of metastases, and extrathyroidal extension (15, 16). *PIK3CA* mutations are uncommon (<2%) in conventional PTC and are
more often found in anaplastic thyroid cancers (9, 10). Concurrent PIK3CA and BRAF mutations appear to have a synergistic effect, resulting in significantly larger tumor size, metastasis, lower disease-free survival (16), and progression from well-differentiated to poorly differentiated thyroid cancer (17).

The best treatment for rare distant metastases is not clear (18). Surgery, radioactive iodine ablation therapy, and external beam radiation have all been employed but may not impact survival rates (5). Targeted therapy with tyrosine kinase inhibitors (TKI) is a newer therapeutic option for the treatment of metastatic, advanced, and RAI-R PTC (7). Lenvatinib is a TKI that decreases tumor growth and cancer progression by inhibiting vascular endothelial growth factor receptors (VEGFR1-3), fibroblast growth factor receptors (FGFR1-4), platelet-derived growth factor receptor alpha, KIT, and RET (19). The SELECT trial demonstrated superiority in progression-free survival compared to placebo (20). The major sites of metastases in trials with lenvatinib were lung and bone (2, 20); less is known about the response to treatment in rare metastatic sites. In one recently reported case of PTC with distant metastases, treatment with lenvatinib significantly reduced lesions in the pancreas, kidney, muscle, and lung with progression-free survival of 8 months (2). Our patient adds to the experience, demonstrating sustained response to full dose lenvatinib for 18 months.

Other therapies are in development to treat RAI-R PTC. Dabrafenib and vemurafenib are BRAF inhibitors that have shown promising results in BRAF V600E-mutated PTC (21). Another treatment in development is MK2206, a novel Akt inhibitor targeting the PIK3/Akt pathway which may benefit patients with PIK3CA mutation (22). Further studies are needed to validate the efficacy of these drugs and develop a therapeutic algorithm for the treatment of these more aggressive PTC variants. Our patient may benefit from both classes of drugs should his response to lenvatinib wane over time.

In summary, this is a rare case of a mixed columnar cell and tall cell variant PTC with BRAF V600E and PIK3CA gene mutation, presenting with rare distant metastases. Optimal treatment for these patients is relatively unknown, but our patient has responded well to treatment with lenvatinib.

Declaration of interest
CH, TR, and VM have no conflicts of interest to declare. JM has received honorarium from EISAI.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contributions statement
CH and VM wrote and reviewed the initial draft of the manuscript. JM reviewed the initial draft of the manuscript and provided the radiological images. TR provided the histological review, pathology description, and images. All authors read and approved the final draft of the manuscript.

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