**1 INTRODUCTION**

Thyroid cancer is among the most commonly diagnosed cancers worldwide, and the incidence is increasing.1 Differentiated thyroid cancers (DTC) account for most of these cases, of which PTC is the most common subtype with favorable 10-year survival of up to 90%–95%.1,2 PTC most commonly presents as an asymptomatic thyroid mass or nodule and less commonly with regional or distant metastasis at onset of diagnosis. Up to 20%–50% of PTC will involve cervical lymphatic spread and 1%–4% involve distant metastasis, with 5-year survival rates reduced to 28% for single-organ and 11% for multi-organ metastasis.3 The majority of patients with metastatic disease...
have single-organ metastasis, most commonly lung (53%), bone (28%), liver (8%), and brain (5%). We present a case of an isolated cerebellar lesion as the presenting feature of metastatic PTC with other unusual features, including an incidental finding of microMTC (medullary thyroid microcarcinoma).

2 | CASE HISTORY/EXAMINATION

An 82-year-old man initially presented with a 6-week history of gradual onset occipital headache, dizziness, and ataxia. MRI brain demonstrated a mixed solid cystic right cerebellar lesion measuring 41 × 41 × 36 mm (Figure 1). It was unclear at this stage whether this represented a primary or metastatic tumor. He denied a history of falls, visual disturbance, weight loss, or other infective symptoms. Neurological examination did not demonstrate cranial nerve abnormalities or focal weakness. An ataxic gait was present in keeping with the location of the metastases. There were no palpable neck lumps, pain, dysphagia, or dysphonia.

Other medical co-morbidities included hypertension, type 2 diabetes, hypercholesterolemia, and reflux. He was a non-smoker, and family history was significant for a niece with a metastatic cancer of unknown primary. ECOG status was 1.

3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND TREATMENT

The patient underwent stereotactic posterior fossa craniotomy and resection of the right cerebellar tumor, which showed fragments of lesional tumor tissue and normal cerebellum. The tumor cells were arranged in papilliform clusters, with the tumor cells conspicuously showing nuclear clearing and overlapping. Some of the nuclei also showed nuclear grooves. On further immunoperoxidase staining, the tumor cells were positive for broad spectrum keratin AE1/AE3, keratin 7, TTF-1, PAX8, HMBE-1, BRAFV600E, and thyroglobulin, while napsin A was negative. Thus, these findings were consistent with a metastatic PTC (Figure 2).

Computed tomography staging demonstrated a mildly bulky left thyroid lobe, mildly prominent left inferior neck lymph node measuring 12 mm, multiple <5 mm nodules within both lung fields, and tiny cystic foci within the liver and kidneys. Thyroid ultrasound showed a 21 × 30 × 22 mm heterogenous hypoechoic nodule with irregular margins and microcalcifications in the inferior pole of the left thyroid lobe (TI-RADS 5) (Figure 3). He was euthyroid, with TSH 1.11 mIU/L and FT4 15.9 pmol/L. Thyroglobulin level was 514 ug/L with negative thyroglobulin antibodies <1.0 IU/ml.

FDG-PET indicated a focus of moderately avid tracer uptake in the left inferior pole of the thyroid gland (SUVmax 4.8) and left-sided cervical lymph nodes, the largest measuring up to 11 mm (SUVmax 2.4). There was relatively reduced uptake in the surgical bed with mildly increased uptake at the resection margins, likely reflecting post-operative changes. There were pulmonary nodules in both lung fields, with the greatest tracer avidity measuring SUVmax 0.9, and no suspicious hilar or mediastinal lymphadenopathy. FNA of the TI-RADS 5 thyroid lesion demonstrated mainly papilliform fragments of malignant cells (Bethesda VI) consistent with PTC.

Multidisciplinary Team meeting recommended the following treatment sequence: (1) total thyroidectomy and left neck dissection, followed by (2) stereotactic radiosurgery to right cerebellar cavity (27 Gray over three fractions) and (3) Radioactive iodine ablation with recombinant TSH stimulation.

Intra-operatively, the tumor nodule detected on thyroid ultrasound and PET scan was determined to be from the left neck level VI rather than the thyroid gland proper, and it was almost completely replaced by a 30-mm nodule of PTC of classical type. There was infiltration into fibro-fatty tissue and skeletal muscle with perineural and multifocal lymphovascular invasion. There was no identifiable...
normal thyroid or lymph node tissue in this tumor nodule (Figure 4a,b). The cells stained positively for BRAF<sup>V600E</sup>, TTF-1, and thyroglobulin. ALK and pan-TRK were negative (Figure 4c). The total thyroidectomy, on the contrary, did not demonstrate evidence of PTC. There were changes of multinodular goiter and interestingly an incidental 4mm focus of calcitonin-positive medullary carcinoma arising from C-cell hyperplasia in the mid-left lobe (Figure 5a,b). As the tumor measured <10mm, this was regarded as medullary microcarcinoma (microMTC) as per WHO classification of Endocrine tumors.4

Since the microMTC was an incidental finding, no pre-operative calcitonin was performed, but a post-operative calcitonin was negative at <5 ng/L (<20). Pre-operative and post-operative parathyroid hormone levels were within the normal range, and clinically there was no recurrent laryngeal nerve palsy. Just prior to the RAI dose, stimulated thyroglobulin was 916 ug/L. The patient underwent 4.22 GBq radioactive iodine ablation with prednisolone to prevent transient edema at the old surgical site.

### 4 | OUTCOME AND FOLLOW-UP

Follow-up MRI brain demonstrated stable post-surgical changes. A post-RAI <sup>131</sup>I scan demonstrated bilateral residual functioning thyroid tissue in the thyroid bed without iodine-avid disease elsewhere. A 6-week follow-up FDG-PET scan demonstrated mildly increased tracer uptake in the left thyroid bed (SUV<sub>max</sub> 3.3) corresponding to a 12mm level IV lymph node and two subcentimeter lymph nodes (SUV<sub>max</sub> 2.5). Two new skeletal foci (SUV<sub>max</sub> 3.6 and 3.7) were also noted in the manubrium and T6 vertebral body. Thyroglobulin continued to be elevated at 620 ug/L with thyroglobulin antibodies <1.0 IU/mL, and calcitonin remained negative. The
patient is currently asymptomatic and awaiting follow-up FDG-PET scan. Treatment of the presumed bony metastasis with intravenous zoledronic acid has been considered.

5 | DISCUSSION

This case of an unusual presentation of PTC with a coincidental microMTC and challenging histopathology has a number of teaching points. Firstly, the presence of brain metastasis in DTC confers poor prognosis, with mean overall survival between 7 and 33 months. Cerebral hemispheres are the most common site of intracranial metastasis, with less common sites being the cerebellum, brainstem, and pituitary. For patients with single brain metastasis and good performance status, surgical resection remains first-line therapy for optimal overall survival, followed by whole brain radiotherapy or stereotactic radiosurgery. Stereotactic radiosurgery for brain metastasis is effective in achieving local control, with median survival of 14 months and shorter survival with higher number of metastases. While RAI is required for treatment of the DTC, uptake by metastatic lesions is overall low, possibly due to reduced expression of the sodium iodine symporter in these lesions. Apart from RAI, tyrosine kinase inhibitors (TKIs) are a class of drugs which directly inhibit mutant protein kinases and are efficacious in RAI-refractory DTC. Genetic profiling in 20 DTC patients with brain metastases revealed the most common mutations as TERT promoter (TERTp) (80%), BRAFV600E (55%), and concurrent mutations (50%). TERTp were associated with poorer
survival, higher prevalence of distant metastases, and RAI-refractory disease.\(^5\) Synergistic effects between coexistent \(TERTp\) and \(BRAF^{V600E}\) mutations also reduces overall survival compared with \(BRAF^{V600E}\) mutation alone.\(^4\)

Up to 10%–15% of all MTCs are incidental findings after thyroidectomy for other indications including PTC.\(^15\) In a large series of 2897 patients undergoing thyroidectomy for PTC, only 11 (0.37%) cases harbored both PTC and MTC, of which all MTC cases were sporadic. Mean PTC tumor size was 1.95 cm compared with 1.20 cm for the MTC component, and none were microMTC.\(^16\) Similarly, incidental MTC prevalence in multinodular goiter specimens is 0.1%–1.3%.\(^15\) There has been debate on the clinical relevance of microMTC and the extent of their management. Distant metastases were found in 5.2% of microMTC cases in one study.\(^17\) Ten-year survival in patients with localized disease was comparable to PTC at 95.7%, but drops with regional (86.7%) or distant metastases (50%), suggesting that microMTCs can be clinically aggressive.\(^17\) While almost all patients with familial MTC harbor \(RET\) germline mutations, in a study of patients with sporadic MTC, the prevalence of somatic \(RET\) mutations ranged from only 11.3% in patients with microMTC up to 58.8% in those with MTC > 3 cm.\(^18\) As the prevalence of \(RET\) mutations is low in microMTC, current ATA guidelines have not recommended routine testing in these patients.\(^19\) While some microMTCs may be clinically significant, there is a paucity of data to fully risk stratify those that occur concurrently with other PTC.

The unusual factor in this case is the absence of PTC in the final thyroidectomy pathology specimen. Intraoperatively, the primary 30 mm PTC was thought to originate from left level VI lymph nodes. Absence of PTC in the thyroidectomy specimen with evidence of metastatic lymph node disease has been rarely reported in the literature and may represent a microcarcinoma unable to be detected by the pathologist.\(^20\) However, this patient presented with sonographic findings of an intrathyroidal nodule with FNA highly consistent with PTC (Bethesda VI) as well as FDG-PET uptake separately in the left thyroid and lymph nodes. It is possible that the PTC had originated from ectopic thyroid tissue that has been overrun by tumor.

6 | CONCLUSION

In summary, we present an unusual case of PTC presenting as a cerebellar metastasis, without an identifiable focus of PTC within the thyroid gland, but rather an extrathyroidal deposit in a left level VI node. An incidental focus of microMTC was present in the thyroidectomy specimen. Management consisted of total thyroidectomy, resection, and radiosurgery of the cerebellar metastasis, and radioactive iodine ablation. There is evidence of new skeletal lesions on follow-up FDG-PET scan suggestive of RAI-refractory disease. This case highlights the rarity of distant metastases in PTC and in particular brain metastasis, which confers poorer prognosis. Such patients may exhibit genetic profiling that is distinct from PTC without distant metastasis. Finally, the presence of microMTC was an unexpected finding. The clinical relevance and risk stratification of incidental microMTC in this setting requires further studies.

AUTHOR CONTRIBUTIONS

MW was involved in the management of the case and wrote the manuscript. SS, SC, and JH was involved in

---

**FIGURE 5** (A) Irregular clusters of medullary thyroid carcinoma cells with clear to faint eosinophilic cytoplasm. These cell clusters were comparatively smaller than adjacent normal follicles and focal amyloid was seen in the left superior corner (H&E stain, x100). (B) Calcitonin stained positively in the carcinoma but also increased number of C cells in adjacent follicles (x20)
the management of the case and assisted with writing of the manuscript. MG assisted with writing and editing of the manuscript. CG was involved in the management of the case and assisted with writing and editing of the manuscript.

ACKNOWLEDGMENT
We acknowledge the care provided by members of the endocrine, neurosurgery, head and neck surgery, radiation oncology, nuclear medicine, and pathology teams involved in this patient’s care.

CONFLICT OF INTEREST
We have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT
Data pertaining to the case report is available upon request.

ETHICAL APPROVAL
This research did not receive any funding from any agency in the public, commercial, or not-for-profit sector. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The patient has kindly consented to the publication of this case, including images. Written consent from the patient and data pertaining to the case is available upon request. Ethics approval was not required as this is a case report.

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

ORCID
Mawson Wang © https://orcid.org/0000-0003-1637-5117

REFERENCES
1. Cabanillas ME, DG MF, Durante C. Thyroid Cancer. Lancet Publishing Group; 2016:2783-2795.
2. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995. Cancer. 1998;83(12):2638-2648.
3. Toraih EA, Hussein MH, Zerfaoui M, et al. Site-specific metastasis and survival in papillary thyroid cancer: the importance of brain and multi-organ disease. Cancers (Basel). 2021;13(7):1625.
4. Lloyd R, Osamura R, Kloppeg G, Rosaj J. WHO Classification of Tumours of Endocrine Organs. 2017.
5. Osborne JR, Kondraciuk JD, Rice SL, et al. Thyroid cancer brain metastasis: survival and genomic characteristics of a large tertiary care cohort. Clin Nucl Med. 2019;44(7):544-549.
6. Al-Dhahri S, Al-Amro AS, Al-Shakwer W, Terkawi AS. Cerebellar mass as a primary presentation of papillary thyroid carcinoma: case report and literature review. Head Neck Oncol. 2009;1:23.
7. Nahed BV, Alvarez-Brekenridge C, Brastianos PK, et al. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Role of Surgery in the Management of Adults with Metastatic Brain Tumors. Oxford University Press; 2019:E152-E155.
8. Bunevicius A, Fribance S, Pikis S, et al. Stereotactic radiosurgery for differentiated thyroid cancer brain metastases: an international. Thyroid. 2021;31(8):1244-1252.
9. Spitzweg C, Bible KC, Hofbauer LC, Morris JC. Advanced Radioiodine-Refractory Differentiated Thyroid Cancer: The Sodium Iodide Symporter and other Emerging Therapeutic Targets. Lancet Publishing Group; 2014:830-842.
10. Gild ML, Tsang VHM, Clifton-Bligh R, Robinson BG. Multikinase inhibitors in thyroid cancer: timing of targeted therapy. Nat Rev Endocrinol. 2021;17(4):225-234.
11. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621-630.
12. Brose MS, Nutting CM, Jarzab B, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319-328.
13. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892-2899.
14. Moon S, Song YS, Kim YA, et al. Effects of coexistent BRAFV600E and TERT promoter mutations on poor clinical outcomes in papillary thyroid cancer: a meta-analysis. Thyroid. 2017;27(5):651-660.
15. Ahmed SR, Ball DW. Incidentally Discovered Medullary Thyroid Cancer. Diagnostic Strategies and Treatment. The Endocrine Society; 2011:1237-1245.
16. Dionigi G, Tanda ML, Piantanida E, et al. Cohesisting medullary and papillary thyroid cancer. J Endocr Surg. 2017;17(2):57.
17. Kazaure HS, Roman SA, Easa JA. Medullary thyroid microcarcinoma: a population-level analysis of 310 patients. Cancer. 2012;118(3):620-627.
18. Romei C, Ugolini C, Cosci B, et al. Low prevalence of the somatic M918T RET mutation in micro-medullary thyroid cancer. J Endocr Surg. 2018;17(4):1625.
19. Wells SA, Asa SL, Dralle H, et al. Revised American thyroid association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.
20. Singh A, Butuc R, Lopez R. Metastatic papillary thyroid carcinoma with absence of tumor focus in thyroid gland. Am J Case Rep. 2013;14:73-75.

How to cite this article: Wang M, Samra S, Chou S, Howle J, Gild ML, Girgis CM. Metastatic papillary thyroid cancer to cerebellum with incidental medullary microcarcinoma. Clin Case Rep. 2022;10:e06207. doi: 10.1002/ccr3.6207