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CASE REPORT

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Metastatic papillary thyroid cancer to cerebellum with incidental medullary microcarcinoma

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Abstract

Thyroid cancer is the most common endocrine cancer, with papillary thyroid carcinoma (PTC) accounting for the majority of these cases. Cerebellar metastasis is rarely the presenting feature and confers poor prognosis. Genetic mutations in this setting are most commonly *TERTp*, in contrast to $BRAF^{V600E}$ in the majority of PTC. We report the case of an 82 year-old male who presented with a symptomatic right cerebellar lesion and underwent surgical resection to demonstrate metastatic PTC. Extensive workup with computed tomography, neck ultrasound and FDG-PET was suggestive of a left thyroid primary lesion, with FNA confirming PTC. However, total thyroidectomy demonstrated incidental microMTC (medullary thyroid microcarcinoma, defined as tumour <10mm) without any evidence of PTC, whereas the left level VI neck dissection demonstrated a 30mm nodule of PTC without identifiable normal thyroid or lymph node tissue.

KEYWORDS

cancer, endocrinology, metastasis, oncology, surgery, thyroid.

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%).[3] 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.

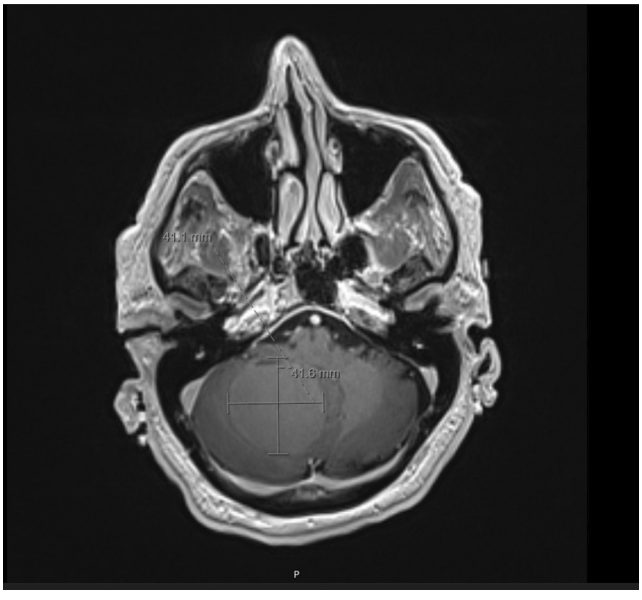

FIGURE 1 MRI brain- 41 × 41 × 36 mm mixed solid cystic lesion in the right cerebellar hemisphere without significant herniation

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, $BRAF^{V600E}$, 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 (SUV_{max} 4.8) and left-sided cervical lymph nodes, the largest measuring up to 11 mm (SUV_{max} 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 SUV_{max} 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 fibrofatty 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*^{V600E}, 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 4 mm focus of calcitonin-positive medullary carcinoma arising from C-cell hyperplasia in the mid-left lobe (Figure 5a,b). As the tumor measured <10 mm, 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.

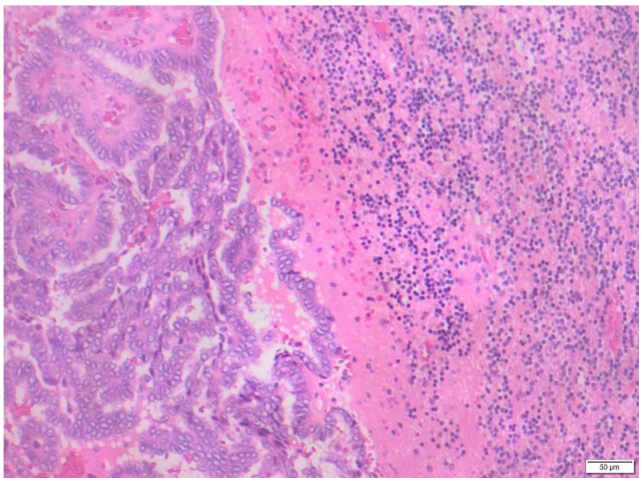

FIGURE 2 Metastatic papillary thyroid carcinoma in cerebellar tissue (Hematoxylin and eosin stain, x100).

4 | OUTCOME AND FOLLOW-UP

Follow-up MRI brain demonstrated stable post-surgical changes. A post-RAI ^{131}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_{max} 3.3) corresponding to a 12 mm level IV lymph node and two subcentimeter lymph nodes (SUV_{max} 2.5). Two new skeletal foci (SUV_{max} 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

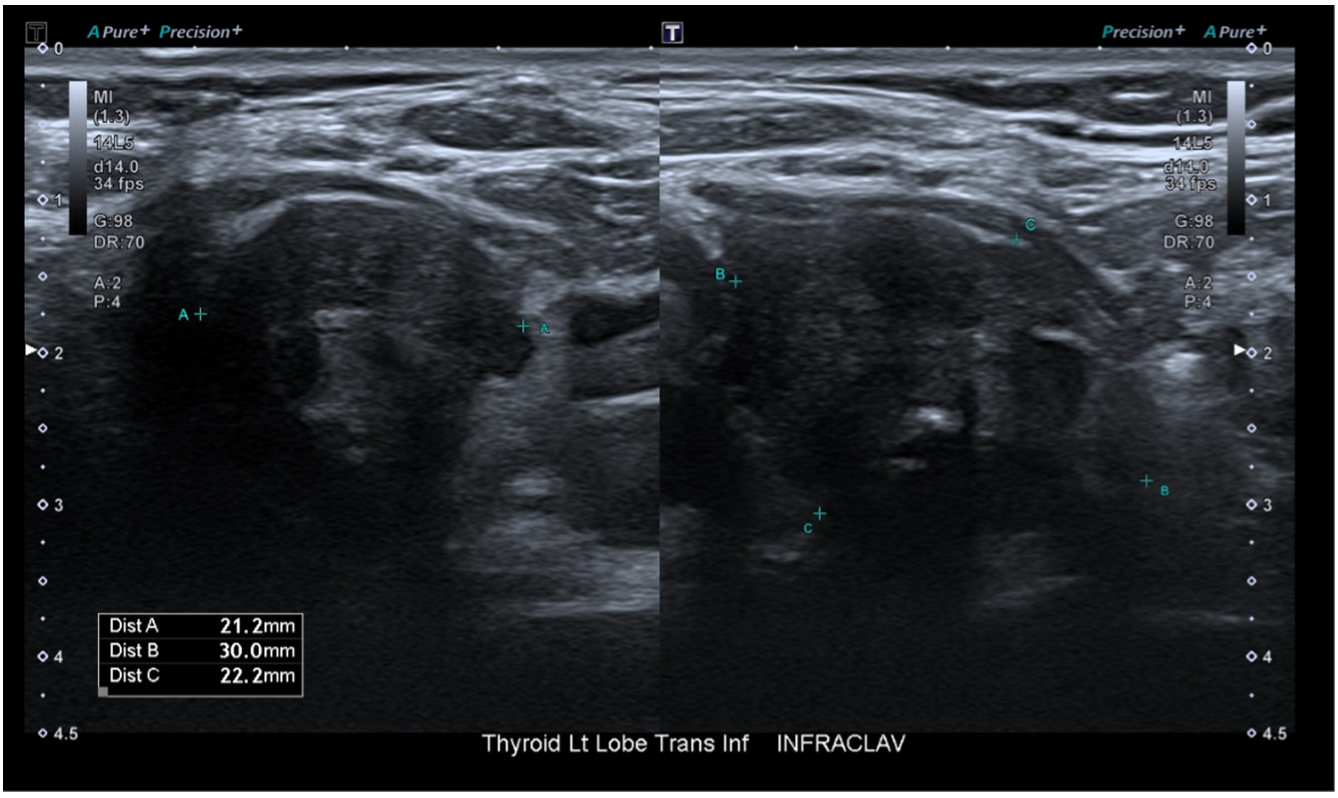

FIGURE 3 Thyroid US- 21 × 30 × 22 mm irregular, hypoechoic nodule with microcalcifications in inferior pole of left thyroid lobe

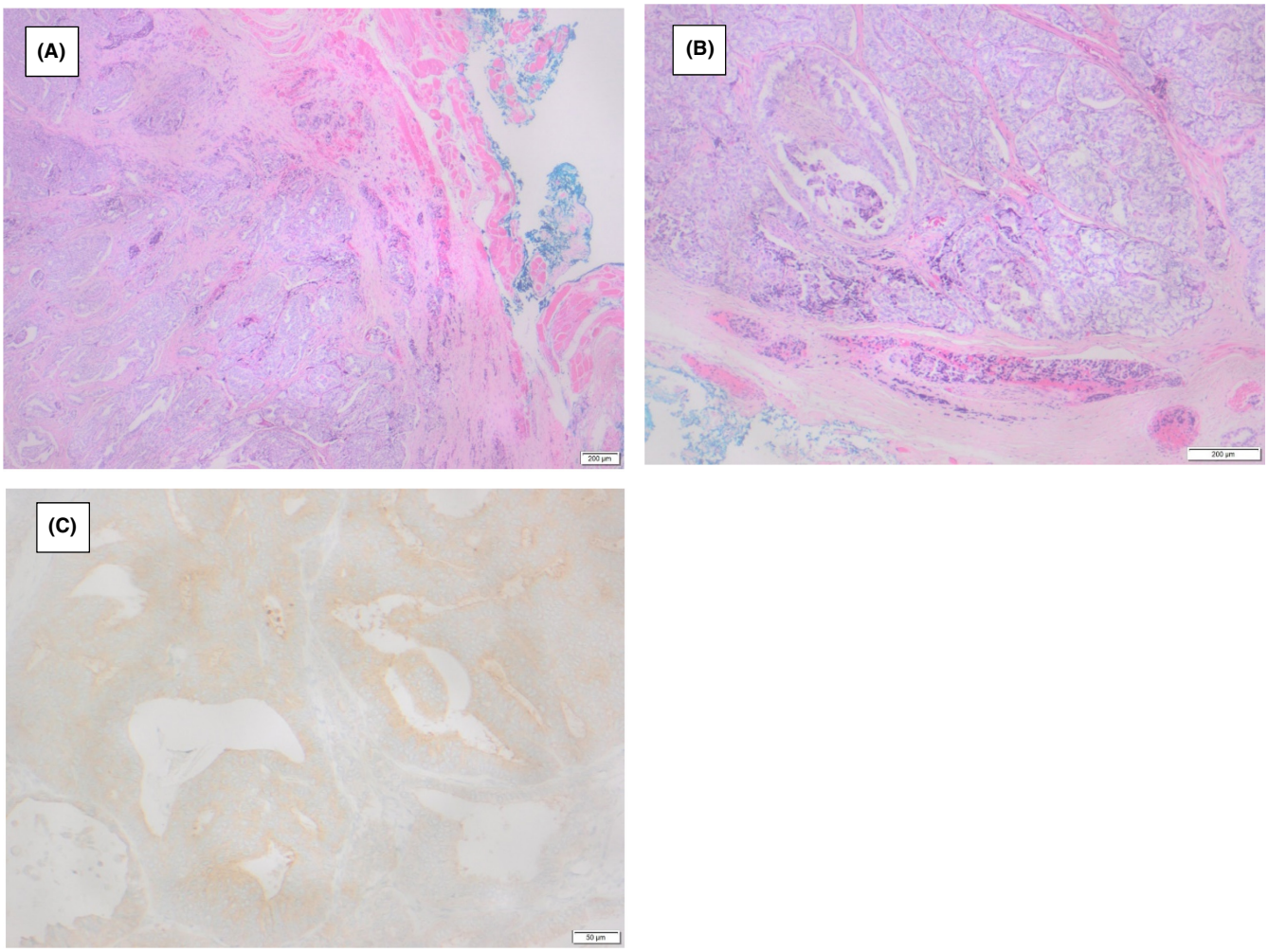

FIGURE 4 (A) Low power view of the left level VI neck tumor where the cells infiltrated into skeletal muscle. No identifiable normal thyroid or lymph node tissue was seen (H&E stain, x20). (B) Area of perineural and lymphovascular invasion in the left level VI tumor (H&E stain, x 40). (C) The papillary thyroid carcinoma stained positively for $BRAF^{V600E}$ (x100)

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.[5] Cerebral hemispheres are the most common site of intracranial metastasis, with less common sites being the cerebellum, brainstem, and pituitary.[6] 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.[7] 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.[8] 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.[9] 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.[10–12] Our patient's FDG-PET scan demonstrated new skeletal lesions that were avid which were not seen on the post-RAI ^{131}I scan, suggestive of RAI-refractory disease. Ten-year survival rates in metastatic DTC with loss of RAI avidity fall to only 10%.[13]

Genetic profiling in 20 DTC patients with brain metastases revealed the most common mutations as TERT promoter (*TERTp*) (80%), $BRAF^{V600E}$ (55%), and concurrent mutations (50%).[5] *TERTp* were associated with poorer

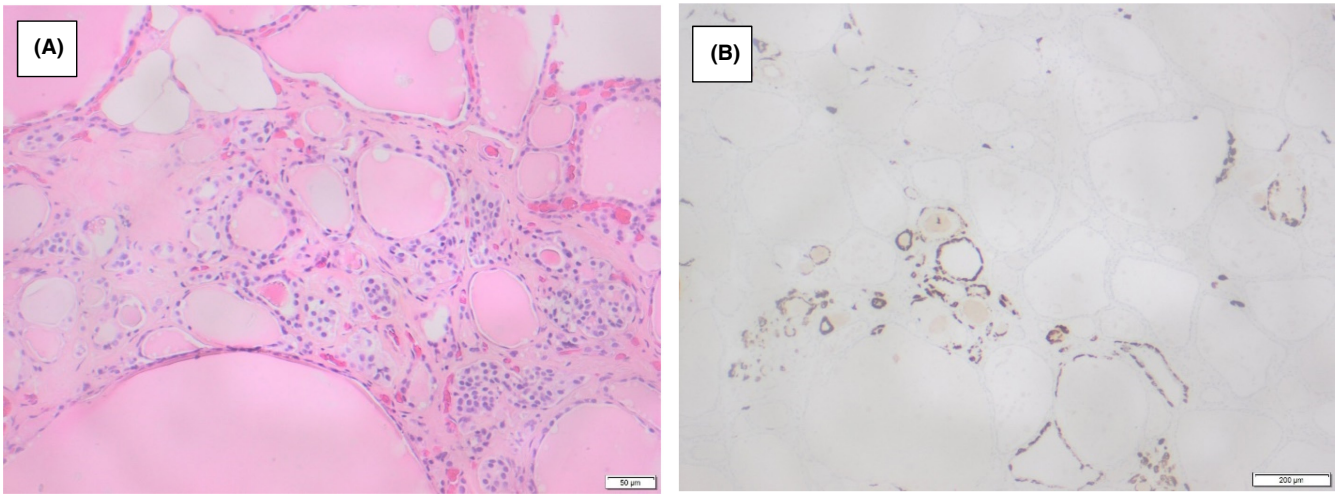

FIGURE 5 (A) Irregular clusters of medullary thyroid carcinoma cells with clear to faint eosinophilic cytoplasm. These cell clusters were comparatively smaller than adjacent normal follicles and focal amyloid was seen in the left superior corner (H&E stain, x100). (B) Calcitonin stained positively in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

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.[14]

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

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.

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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.

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