Metastatic papillary thyroid cancer to cerebellum with incidental medullary microcarcinoma

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Abstract

Papillary thyroid carcinoma (PTC) accounts for the vast majority of thyroid cancer cases. Cerebellar metastasis is rarely the presenting feature. We report a patient presenting with a cerebellar lesion which demonstrated metastatic PTC upon resection, with unusual features including incidental medullary thyroid microcarcinoma without PTC in the main thyroidectomy specimen.

Title Page

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Ethics and Integrity Policies

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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.

Title of case report or series

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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 favourable 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).

Case History/Examination

An 82 year-old male 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 41x41x36mm (**Image 1**). 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, hypercholesterolaemia 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.

Differential diagnosis, investigations and treatment

The patient underwent stereotactic posterior fossa craniotomy and resection of the right cerebellar tumour, which showed fragments of lesional tumour tissue and normal cerebellum. The tumour cells were arranged in papilliform clusters, with the tumour cells conspicuously showing nuclear clearing and overlapping. Some of the nuclei also showed nuclear grooves. On further immunoperoxidase staining the tumour 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 (**Image 2a).**

Computed tomography staging demonstrated a mildly bulky left thyroid lobe, mildly prominent left inferior neck lymph node measuring 12mm, multiple <5mm nodules within both lung fields, and tiny cystic foci within the liver and kidneys. Thyroid ultrasound showed a 21x30x22mm heterogenous hypoechoic nodule with irregular margins and microcalcifications in the inferior pole of the left thyroid lobe (TI-RADS 5) (**Image 3**). He was euthyroid, with TSH 1.11mIU/L and FT4 15.9pmol/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 11mm (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 3 fractions) and 3) Radioactive iodine ablation with recombinant TSH stimulation.

Intra-operatively, the tumour 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 30mm 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 tumour nodule (**Image 2b/c**). The cells stained positively for$BRAF^{V600E}$, TTF-1 and thyroglobulin. ALK and pan-TRK were negative (**Image 2d**). The total thyroidectomy on the other hand did not demonstrate evidence of PTC. There were changes of multinodular goitre and interestingly an incidental 4mm focus of calcitonin-positive medullary carcinoma arising from C-cell hyperplasia in the mid left lobe (**Image 4a/b**). As the tumour measured <10mm, this was regarded as medullary microcarcinoma (microMTC) as per WHO classification of Endocrine tumours[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). 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 oedema at the old surgical site.

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 six-week follow-up FDG-PET scan demonstrated mildly increased tracer uptake in the left thyroid bed (SUV_{max}3.3) corresponding to a 12mm level IV lymph node and two subcentimetre 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. The patient is currently asymptomatic and awaiting follow-up FDG-PET scan. Treatment of the presumed bony metastasis with intraveoous zoledronic acid has been considered.

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 7-33 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 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 to $BRAF^{V600E}$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 harboured both

PTC and MTC, of which all MTC cases were sporadic. Mean PTC tumour size was 1.95cm compared to 1.20cm 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 localised 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 >3cm[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. Intra-operatively, the primary 30mm 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 tumour.

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: was involved in the management of the case and assisted with writing of the manuscript

SC: 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.

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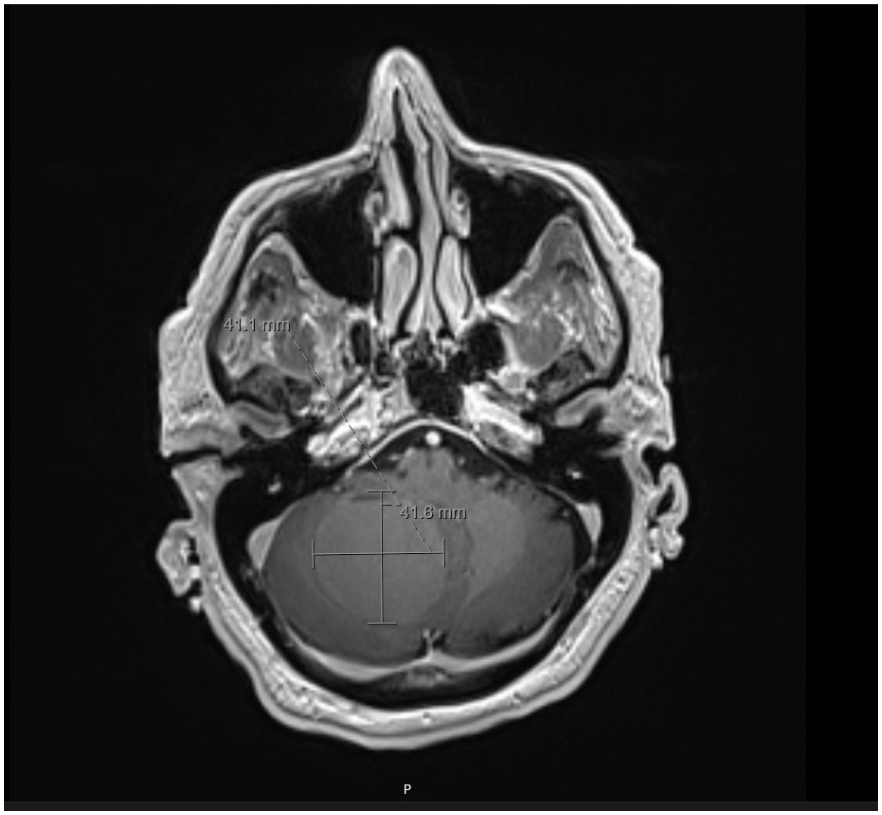
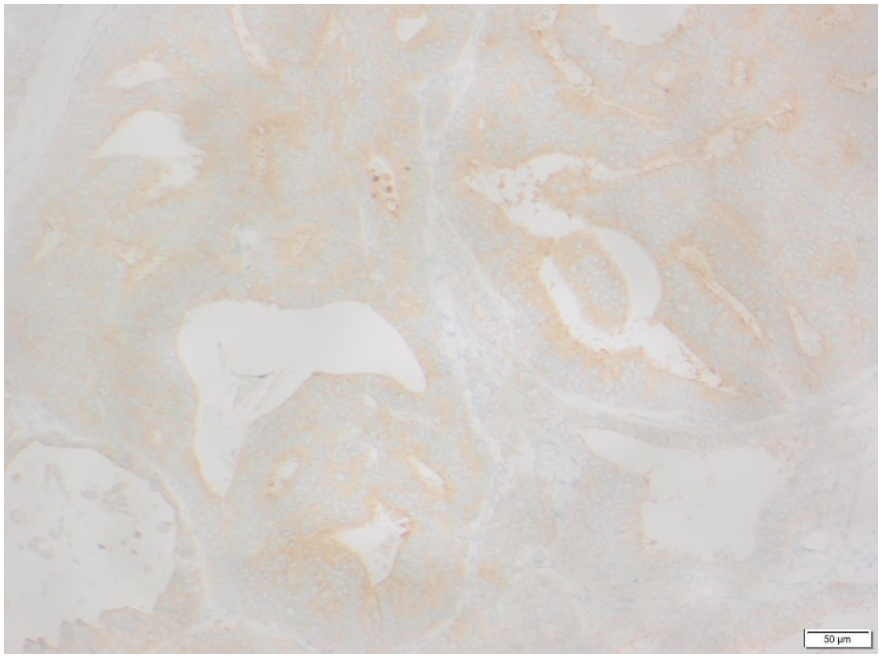
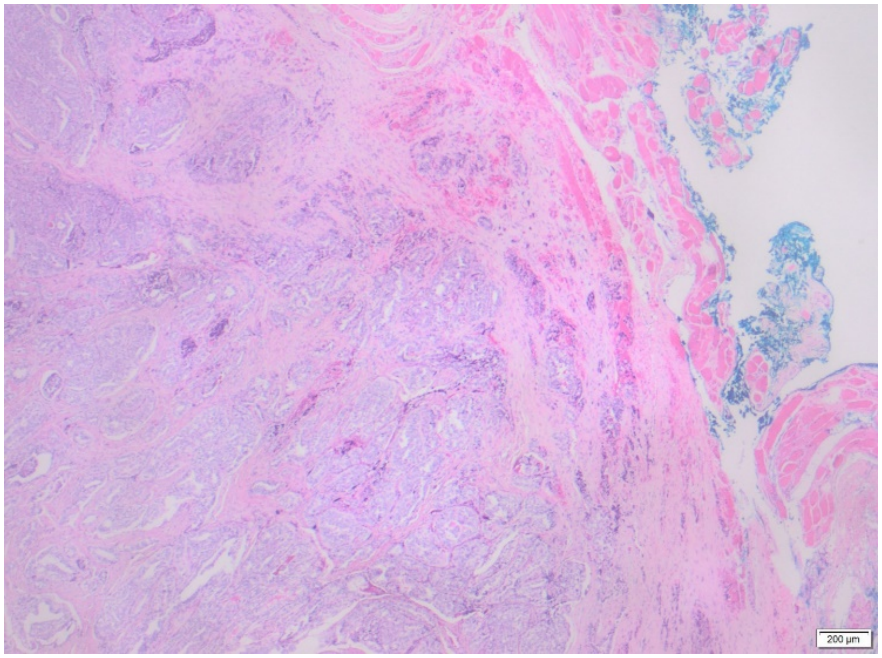
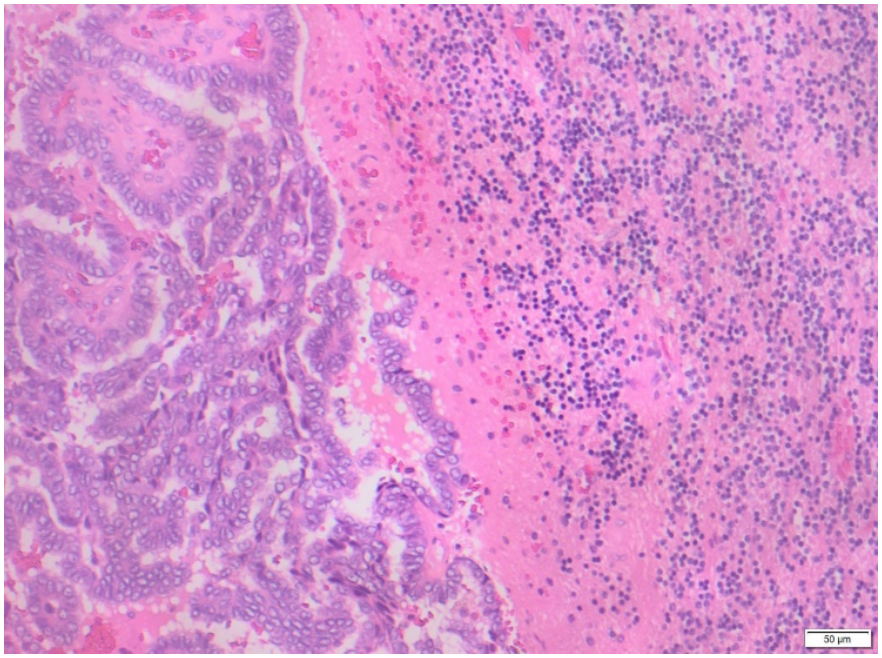
Images

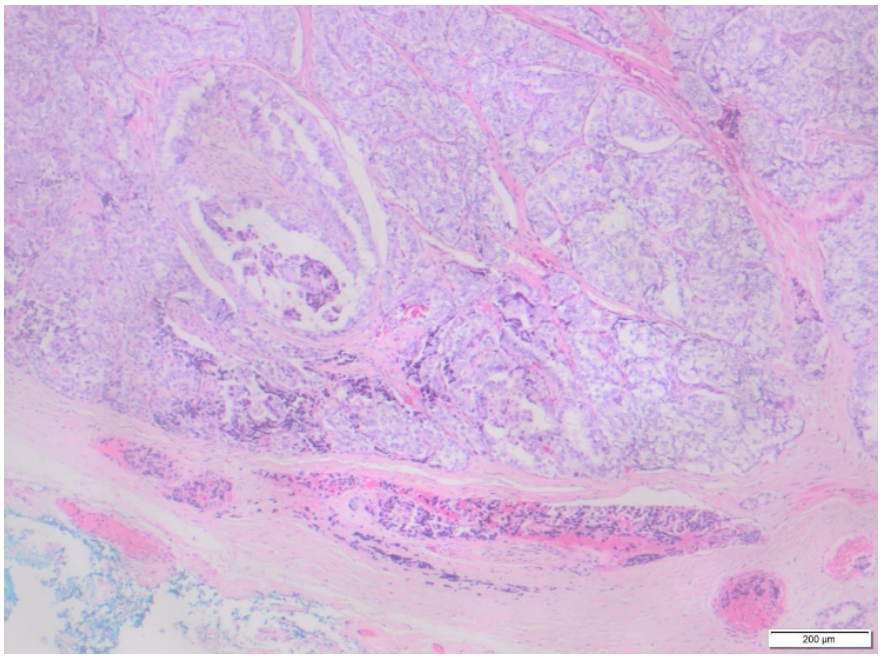


1. MRI brain- 41x41x36mm mixed solid cystic lesion in the right cerebellar hemisphere without significant herniation.

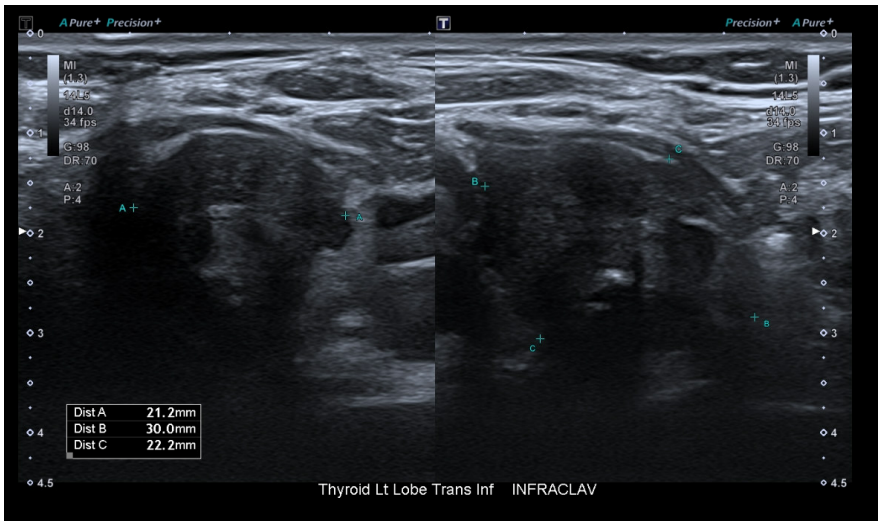




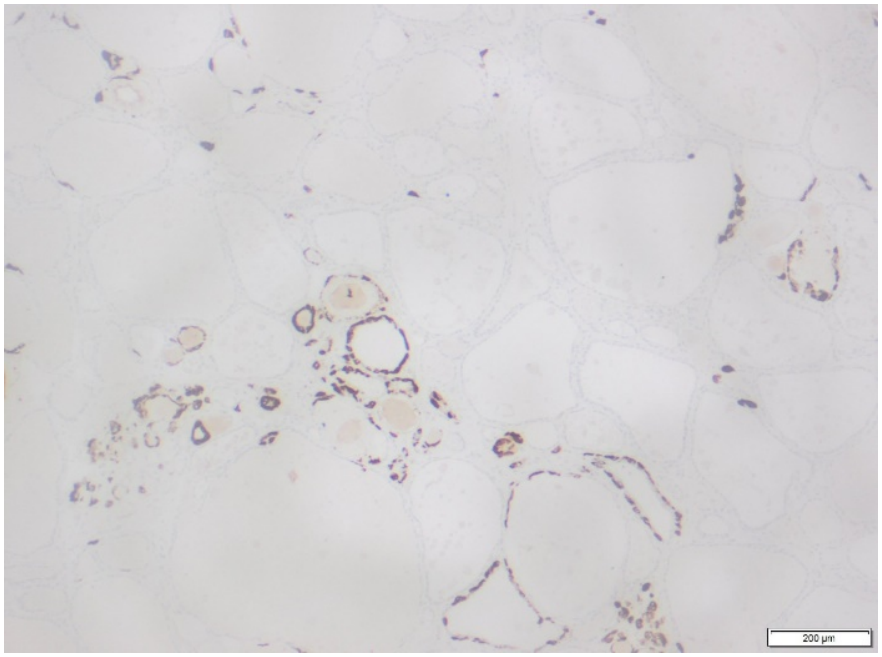


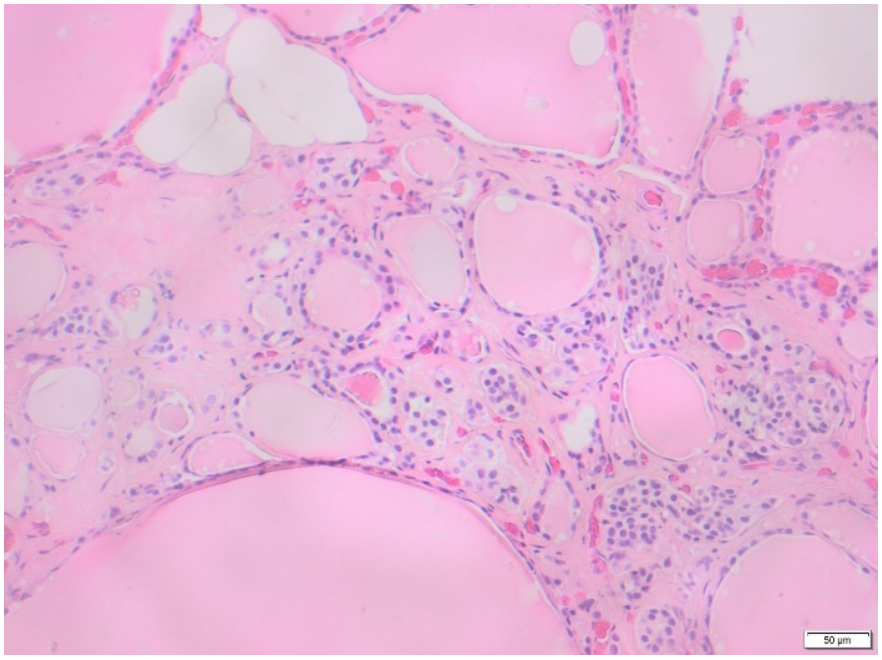


2a. Metastatic papillary thyroid carcinoma in cerebellar tissue (Haematoxylin and eosin stain, x100). 2b. Low power view of the left level VI neck tumour where the cells infiltrated into skeletal muscle. No identifiable normal thyroid or lymph node tissue was seen (H&E stain, x20). 2c. Area of perineural and lymphovascular invasion in the left level VI tumour (H&E stain, x 40). 2d. The papillary thyroid carcinoma stained positively for $BRAF^{V600E}$ (x100).



3. Thyroid US- 21x30x22mm irregular, hypoechoic nodule with microcalcifications in inferior pole of left thyroid lobe





4a. 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).

4b. Calcitonin stained positively in the carcinoma but also increased number of C cells in adjacent follicles (x20).

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