Rare disease

Brain metastasis from medullary thyroid carcinoma

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Summary

The brain is an exceedingly rare site of metastasis in medullary thyroid carcinoma (MTC). A 50-year-old female who had a history of micro-MTC 11 years prior developed a cerebellar metastasis which was incidentally discovered. Imaging revealed a right cerebellar hemispheric mass with contrast enhancement on CT scans. Histopathologic exam demonstrated a metastatic tumour composed of nodules and sheets of large tumour cells with abundant cytoplasm. Immunohistochemistry confirmed the origin from a MTC. This case report highlights the unique features of an unusual metastatic brain tumour, which followed an indolent course for a long time despite multiple distant metastases.

BACKGROUND

Medullary thyroid carcinoma (MTC) constitutes 5–10% of all thyroid carcinomas¹ and is the third most common type of thyroid cancer following papillary and follicular carcinomas.² It is derived from the parafollicular C cells and in this regard differs from the follicular cell-derived papillary and follicular carcinomas both clinically and pathologically.³ MTC exhibits a more aggressive clinical behaviour and is more difficult to treat.⁴ This is in contrast to papillary and follicular carcinomas, which respond to radioactive iodine and therefore may have a favourable clinical course, even in case of recurrence or metastasis.⁵ MTC <1 cm in size are typically referred to as ‘micro-MTC’. Regional lymph nodes are the most common sites of metastasis for MTC. They are involved in 50% of cases at the time of presentation.^{1,3} When distant metastasis occurs, the most frequently involved organs are liver, lung, bone and mediastinum.^{2,3} Brain metastasis occurs in approximately 1% of all cases of thyroid carcinoma.^{6,7} Most of these are follicular carcinomas. Brain metastasis from MTC is exceedingly uncommon, with only 10 previously reported cases (see table 1).

CASE PRESENTATION

A 37-year-old female was diagnosed with micro-medullary carcinoma of the thyroid in 1998. Her initial presentation was due to enlargement of cervical lymph nodes. Cytologic examination of a fine-needle aspiration from the lymph nodes identified MTC. She underwent a total thyroidectomy, bilateral neck dissection as well as mediastinal dissection. The diagnosis was histologically confirmed. The tumour was composed of cells with abundant eosinophilic cytoplasm that had poorly defined cell borders (figure 1). The nuclei had normochromatic chromatin with ‘salt and pepper’ appearance. Immunohistochemistry revealed reactivity for carcinoembryonic antigen (CEA), chromogranin, calcitonin and calcitonin gene related peptide (CGRP). The primary tumour was identified in the right lobe of the thyroid gland. It was one irregular and poorly demarcated

nodule measuring 0.6 cm. Histologic evaluation revealed MTC. Multiple foci of vascular invasion were identified (figure 1C). There was no evidence of underlying C cell hyperplasia in either lobe. Multiple metastases were found in cervical and mediastinal lymph nodes (32 of 63 nodes). There was evidence of extracapsular tumour extension in one of the lymph nodes from the right neck dissection. The patient had no familial history of multiple endocrine neoplasia (MEN). Therefore, germline genetic testing was only performed for the RET proto-oncogene, which did not identify a mutation.

INVESTIGATIONS

Tissue preparation and immunohistochemistry

Tissue was fixed in 10% neutral buffered formalin and embedded in paraffin. For light microscopy, 4 µm-thick sections were stained with H&E. Immunohistochemistry was also performed on 4 µm-thick sections. Slides were deparaffinised and rehydrated in xylene, then microwaved in 10 mmol/l citrate buffer. All sections were counterstained with hematoxylin. For all slides, controls included positive controls on known positive material and negative controls by omission of the primary antibody. After microwave antigen retrieval, immunolocalisation was performed with the primary antibody and the streptavidin-biotin peroxidase complex technique and 3,3-diaminobenzidine. The Ki-67 (MIB-1) antibody was obtained from Dako (Carpinteria, California, USA) and used at a dilution of 1:100. The antibody for chromogranin, calcitonin and thyroid transcription factor 1 (TTF-1) (prediluted) were from Ventana (Ventana Medical Systems, Tucson, Arizona, USA). The CGRP antibody was obtained from Serotec (Oxfordshire, UK) and used at a dilution of 1:1000. The dilution for the monoclonal CEA Clone B80.1 (Biomedica, Foster City, California, USA) was 1:5000. All immunohistochemical studies were performed in a Ventana automated stainer. For evaluation of MIB-1 immunohistochemistry, the number of positive nuclei per 1000 cells was scored.

Figure 1 Histopathology of the original primary thyroid tumour: (A) at low-power magnification, the tumour is composed of nodules and elicits a desmoplastic reaction in the surrounding thyroid tissue. (B) Higher magnification shows that tumour cells have round nuclei with normochromatic chromatin and a large amount of eosinophilic cytoplasm. (C) Multiple foci of vascular invasion were present.

Histopathology

Histopathologic examination of the neurosurgical specimen revealed a metastatic carcinoma composed of sheets and nodules of large cells with abundant cytoplasm and round nuclei. There were frequent areas of comedo-type necrosis (figure 2A). Mitoses were infrequent, at less than 1/10 high-power fields (figure 2B). Immunohistochemistry

Figure 2 Histopathology of the tumour (low power; 5 $\times$; H&E): (A) a sharp border is present between metastatic tumour and normal cerebellum (bottom). It forms nests of monotonous cells with central comedo-type necrosis. (B) Higher magnification (40 $\times$; H&E) reveals that tumour nodules are composed of sheets of monotonous cells with indiscernible cytoplasmic borders and normochromatic, round to oval nuclei with occasional nucleoli.

revealed strong expression of chromogranin (figure 3A) and partial and weak expression of calcitonin and CGRP (figure 3B,C). Diffuse immunoreactivity with antibodies to CEA was also observed (figure 3D). Most of the tumour-cell nuclei were positive with TTF-1 (figure 3E), supporting the thyroid origin of the tumour. The MIB-1 labelling index was less than 1% (figure 3F).

OUTCOME AND FOLLOW-UP

Calcitonin levels declined from >100 000 ng/l (normal <100 ng/l) preoperatively to 42 900 ng/l 3 months postoperatively. CEA levels, however, remained persistently elevated at 39 μ g/l (normal <3 μ g/l). A CT scan 1 month after her surgery revealed a liver mass of 2.8 cm and a small, sclerotic lesion in the third lumbar vertebra. In light of the persistently elevated CEA (39 μ g/l; normal <3 μ g/l), these lesions were interpreted as evidence of metastatic disease. The patient, who was completely asymptomatic, received somatostatin analogue and interferon for 1 year postoperatively. This was discontinued due to lack of structural disease regression on serial imaging studies. She was followed regularly by CT scans including the brain until June 2007, when a mass in her cerebellum

Figure 3 Immunohistochemistry: (A) tumour cells show diffuse cytoplasmic positivity with chromogranin, (B) cytoplasmic positivity with calcitonin and (C) focal cytoplasmic positivity with calcitonin gene related peptide (CGRP). (D) diffuse and ubiquitous immunoreactivity was observed with the monoclonal antibody to carcinoembryonic antigen (CEA). (E) Strong nuclear positivity with thyroid transcription factor 1 (TTF-1) was detected in the majority of cells (F) and proliferative activity demonstrated by ki-67 (MIB-1) was less than 1%.

Figure 4 Cranial MRI at the level of cerebellum: (A) T1-weighted axial scan after gadolinium shows a homogeneously enhancing intra-axial lesion within the right cerebellar hemisphere. (B) Fast-spoiled gradient echo image after gadolinium administration demonstrates that the mass extends from the midline into the right cerebellar hemisphere.

was detected. MRI images displayed a homogeneously enhancing intra-axial mass in the right cerebellar hemisphere, measuring of 2.3 cm (figure 4). The tumour was resected following a midline suboccipital incision. The patient subsequently enrolled in a clinical trial of the tyrosine kinase inhibitor vandetanib until the spring of 2009. As of September 2010, there is no evidence of disease progression. The resection site in the cerebellum showed no evidence of recurrence and no abnormal enhancement. There was no evidence of other metastatic disease in the brain.

DISCUSSION

MTC is the third most common type of thyroid cancer.² It constitutes 5–10% of all malignant thyroid tumours.¹

MTC originates from the parafollicular C cells^{1 3} and has histopathologic and clinical characteristics that differ from those of papillary and follicular carcinomas of thyroid origin.³ Papillary and follicular carcinomas characteristically have a slow growth rate with only very rare fatal outcome due to the availability of targeted therapy with radioactive iodine.⁶ MTC is typically a more aggressive form of thyroid cancer with higher rate of recurrence and increased mortality.^{4 7} The typical sites of metastasis of medullary thyroid cancer are the regional lymph nodes, which are frequently involved at the time of diagnosis. Upper and anterior mediastinal lymph nodes are also in the pathway of tumour spread.¹ Sites of distant metastases are typically lung, liver and bone.^{2 3} Metastasis to adrenal glands, pleura, heart, ovary and pancreas has also been reported.²

Table 1 Summary of previously reported cases of medullary thyroid carcinoma with brain metastases

Authors	Age, gender	Location of tumour	Additional metastatic site(s)	Duration between primary diagnosis and brain metastasis	Association with familial/syndromic disease
Timothy <i>et al</i> ¹	67 Years, F	Left cerebellar hemisphere, fourth ventricle and right cerebellar hemisphere	Locoregional lymph nodes	4 Years	Not mentioned
Chiu <i>et al</i> ^{9*}	50 Years, F	Not mentioned	Brain, lung, bone, locoregional lymph nodes	4.3 Years	Not mentioned
Salvati <i>et al</i> ⁶	51 Years, F	Temporal	Lung	4 Years	Not mentioned
McWilliams <i>et al</i> ⁶	34 Years, F	Not mentioned	Locoregional lymph nodes	14 Years	Not mentioned
Pitale <i>et al</i> ¹¹	42 Years, M	Left frontal-parietal lobe and cerebellum	Multiple systemic metastases	25 Years	MEN2A
Mikami <i>et al</i> ¹⁰	55 Years, F	Left temporal gyrus	Neck and trachea	19 Years	Not mentioned
Kabir <i>et al</i> ⁷	57 Years, F	Right Meckel's cave and cavernous sinus	Not mentioned	25 Years	None (history of parathyroidectomy)
Williams <i>et al</i> ¹²	23 Years, F	Pituitary	lung and bone	15 Years	MEN2b
Bhatoe <i>et al</i> ¹³	38 Years, M	Pituitary	None	6 Months	Not mentioned

*Information is gathered from a case series, therefore the numerical data are median values.
F, female; M, male; MEN, multiple endocrine neoplasia.

Even though thyroid cancer, in general, is a common malignancy, only 1% of all thyroid carcinomas metastasise to brain.^{6–8} Of patients with thyroid carcinoma, those with metastatic spread to brain are typically older, have larger primary tumours and show evidence of extrathyroidal extension as well as distant metastasis at initial cancer diagnosis.^{6,9} Brain metastasis from thyroid carcinoma is also more commonly seen with histologically more aggressive types, such as anaplastic or oxyphilic carcinoma. As with other tumours that metastasise to brain, cases of thyroid cancer with brain metastasis have a poor prognosis.⁹

MTC metastatic to the brain is an exceedingly rare entity with only 11 previously reported cases in the literature (see table 1).^{2,6–10,12,13} The first reported case was that of a 67-year-old female patient who had multiple cerebellar metastases from MTC 3 years after the initial diagnosis. She had extensive lymph node involvement at the time of diagnosis but no evidence of other distant metastasis. The largest cerebellar mass was surgically removed and the diagnosis of a MTC was made histologically.² A more clinically oriented study on the prognosis and treatment of brain metastases from thyroid carcinoma also included four cases of metastatic medullary carcinoma. In one of these, brain metastasis was found on postmortem examination while the other three cases were diagnosed during follow-up. All of these cases had locoregional lymph node metastasis and three had distant metastases in organs other than the brain. The median interval from the time of initial diagnosis to detection of brain metastasis was 4.3 years.⁹ Another study reviewing 12 cases of thyroid cancers metastatic to brain⁸ mentioned a 51-year-old female patient with MTC who had a brain metastasis 4 years after initial diagnosis. She also had pulmonary involvement. In another review, a 34-year-old female with local lymph node involvement developed a brain metastasis 14 years after diagnosis.⁶ In another case report, one patient with MEN syndrome and metastatic MTC to brain was a 42-year-old male who had multiple foci of cerebral and cerebellar involvement. There was tumour metastasis to regional lymph nodes at presentation and he was diagnosed with brain metastases after being followed-up for 25 years. Brain involvement in this patient was a component of multiple metastases.¹¹ Another patient was a 55-year-old

female who was followed for 19 years without symptoms and had recurrence in the neck and around the trachea, followed by brain metastasis.¹⁰ A 57-year-old male who developed intracranial metastasis after 25 years of uneventful follow-up with no indication of systemic spread.⁷ The tumour was extradural, arising from the petrous apex and invading the cavernous sinus. The two most recently reported cases were both MTC metastatic to the pituitary gland,^{12,13} and both patients presented with visual loss. One patient was a 23-year-old woman with MEN2b who also had with diabetes insipidus.¹² A 38-year-old male had a history of resection of pituitary adenoma 5 years earlier.¹³ These reported cases are consistent with the general observations that brain metastasis from thyroid carcinomas are more likely to occur in older patients with bulky disease and systemic spread.¹⁴

Learning points

- Brain metastasis from MTC is exceptionally rare.
- The case presented here is unusual because of the unexpected distant metastatic site for a MTC. The patient had metastatic disease at the time of initial presentation and developed cerebellar metastasis after 9 years of follow-up.
- The tumour appears to have a very slow growth rate and has been stable for many years despite the presence of systemic disease.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Fialkowski EA, Moley JF. Current approaches to medullary thyroid carcinoma, sporadic and familial. *J Surg Oncol* 2006;**94**:737–47.
2. Timothy J, Kerawala C, Brazil L, *et al*. Medullary cell carcinoma of the thyroid: metastases to the central nervous system. *Eur J Surg Oncol* 1995;**21**:329–30.
3. Wilson PC, Millar BM, Brierley JD. The management of advanced thyroid cancer. *Clin Oncol (R Coll Radiol)* 2004;**16**:561–8.
4. Dionigi G, Bianchi V, Rovera F, *et al*. Medullary thyroid carcinoma: surgical treatment advances. *Expert Rev Anticancer Ther* 2007;**7**:877–85.
5. Kobayashi T, Asakawa H, Tamaki Y, *et al*. Fatal differentiated thyroid cancer. *J Surg Oncol* 1996;**62**:123–7.

6. **McWilliams RR**, Giannini C, Hay ID, *et al.* Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years. *Cancer* 2003;**98**:356–62.
7. **Kabir SM**, Zafar MS, Brydon HL. Intracranial metastasis from medullary carcinoma of the thyroid 25 years after primary surgery. *Br J Neurosurg* 2006;**20**:169–72.
8. **Salvati M**, Frati A, Rocchi G, *et al.* Single brain metastasis from thyroid cancer: report of twelve cases and review of the literature. *J Neurooncol* 2001;**51**:33–40.
9. **Chiu AC**, Delpassand ES, Sherman SI. Prognosis and treatment of brain metastases in thyroid carcinoma. *J Clin Endocrinol Metab* 1997;**82**:3637–42.
10. **Mikami T**, Niwa J, Kubota T, *et al.* Solitary brain metastasis from medullary carcinoma of the thyroid. *No Shinkei Geka* 2003;**31**:905–9.
11. **Pitale SU**, Melian E, Thomas C, *et al.* Brain metastases from medullary thyroid carcinoma in a patient with multiple endocrine neoplasia type 2A. *Thyroid* 1999;**9**:1123–5.
12. **Williams MD**, Asa SL, Fuller GN. Medullary thyroid carcinoma metastatic to the pituitary gland: an unusual site of metastasis. *Ann Diagn Pathol* 2008;**12**:199–203.
13. **Bhattoe HS**, Badwal S, Dutta V, *et al.* Pituitary metastasis from medullary carcinoma of thyroid: case report and review of literature. *J Neurooncol* 2008;**89**:63–7.
14. **Biswai BM**, Bai CS, Sandhu MS, *et al.* Management of intracranial metastases of differentiated carcinoma of thyroid. *J Neuro Oncol* 1994;**22**:77–81.

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