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Tumor-to-Tumor Metastasis of Medullary Thyroid Carcinoma to Paraganglioma in a Multiple Endocrine Neoplasia Type 2B Patient: A Case Report and Literature Review

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Tumor-to-tumor metastasis is a rare phenomenon in which primary tumor cells metastasize to other tumors. Herein, we report an extremely rare case of tumor-to-tumor metastasis of medullary thyroid carcinoma to a paraganglioma in a patient with multiple endocrine neoplasia type 2B. Based on genetic examination, a 36-year-old woman was diagnosed with multiple endocrine neoplasia type 2B when she was 24 years old. She had a history of total thyroidectomy for medullary thyroid carcinoma and bilateral adrenalectomy for pheochromocytomas, which were performed when she was 15 years and 29 years old, respectively. Follow-up computed tomography demonstrated a retroperitoneal tumor of 30 mm in diameter beside the left kidney and a liver tumor of 16 mm in diameter located in segment 6. The retroperitoneal and liver tumors were surgically resected and examined by a pathologist. Histological examination revealed the classic Zellballen pattern in the retroperitoneal tumor, rendering the diagnosis of a paraganglioma recurrence. Inside the tumor, a white nodule positive for carcinoembryonic antigen, weakly positive for calcitonin, and negative for tyrosine hydroxylase, was identified and diagnosed as a metastatic medullary thyroid carcinoma with high malignant potential. The liver lesion was diagnosed as a metastasis of the medullary thyroid carcinoma. This is the first report of tumor-to-tumor metastasis of medullary thyroid carcinoma to paraganglioma in a patient with multiple endocrine neoplasia type 2B twenty years after total thyroidectomy.

Keywords: calcitonin; medullary thyroid carcinoma; multiple endocrine neoplasia type 2B; paraganglioma; tumor-to-tumor metastasis
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Introduction

Tumor-to-tumor metastasis (TTM), in which primary tumor cells metastasize to other tumors, is extremely rare. Owing to the limited number of reports, the underlying mechanisms of TTM remain unclear. Pathologically, the diagnosis is confirmed only when the following diagnostic criteria are met: (i) more than one primary tumor exists; (ii) the recipient tumor is a true benign or malignant neoplasm; (iii) the metastatic neoplasm is a true metastasis with established growth in the host tumor, not the result of contiguous growth (collision tumor) or embolization of donor tumor cells; and (iv) tumors that have metastasized to the lymphatic system are excluded (Campbell et al. 1968; Petraki et al. 2003).

Lung, breast, colorectal, and prostate carcinomas and malignant melanoma have been reported as donor tumors (Shariff et al. 2009; Hashimoto et al. 2011; Matsukuma et al. 2013; Sayegh et al. 2015; Wu and Pan 2015; Cavalcante et al. 2018; Tan et al. 2019; Luo et al. 2020), and renal cell carcinoma, meningiomas, thyroid neoplasms, pituitary adenomas, and gliomas have been reported as recipient tumors

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(Fried 1930; Williams et al. 2008; Yu et al. 2009; Moody et al. 2012; Erdogan et al. 2014; Song et al. 2017; Fioravanzo et al. 2019). Donor tumors are generally more aggressive than recipient tumors, which are often benign or indolent.

Multiple endocrine neoplasia type 2B (MEN 2B) is a rare, autosomal dominant disease characterized by synchronous and metachronous multiple endocrine tumors, such as medullary thyroid carcinoma (MTC), pheochromocytoma/paraganglioma, mucosal neuromas, and intestinal ganglioneuroma (O'Riordain et al. 1995; Castinetti et al. 2018). The diagnosis is confirmed through genetic examination when a mutation in the *rearranged during transfection (RET)* protooncogene is observed. Patients with MEN 2B develop MTC, which is more aggressive than other hereditary and sporadic MTC types. Therefore, patients with MEN 2B have a worse prognosis than those with MEN 2A (10-year survival of MEN 2B, 75.5% vs. MEN 2A, 97.4%) (Modigliani et al. 1998). MTC in MEN 2B is a life-threatening tumor with high malignancy, and prophylactic resection of the thyroid is recommended when patients are diagnosed with MEN 2B (Castinetti et al. 2019).

Here, we report a patient with MEN 2B presenting TTM from MTC 20 years after total thyroidectomy.

Case Presentation

The patient was a 36-year-old woman diagnosed with MEN 2B when she was 24 years old. At 15 years old, she was diagnosed with MTC and underwent total thyroidectomy, parathyroidectomy, and bilateral cervical lymph node (CLN) dissection. As mucosal neuromas were also observed around the lips, MEN 2B was strongly suspected. Genetic examination revealed mutations in the *RET* oncogene, which confirmed the diagnosis of sporadic MEN 2B. At the age of 29 years, elevation of blood pressure was observed. Upon examination, she was diagnosed with bilateral pheochromocytoma, and laparoscopic bilateral adrenalectomy was performed. The patient underwent CLN resection for MTC recurrence.

After surgery, careful follow-up with computed tomography (CT) and blood tests for carcinoembryonic antigen (CEA) and calcitonin levels were performed. Although CT detected no obvious lesions, CEA and calcitonin levels remained high.

When she was 36 years old, enhanced CT revealed a retroperitoneal mass of 30 mm in diameter at the upper pole of the left kidney (Fig. 1A). This tumor contained a low-density area in the central part that represented necrotic tissue. Enhanced magnetic resonance imaging showed a tumor in the retroperitoneum and a hepatic low-intensity mass, 16 mm in diameter, located in segment 6. ^{123}I-metaiodobenzylguanidine scintigraphy demonstrated accumulation of a radioisotope in the retroperitoneum (Fig. 1A). The levels of CEA and calcitonin were 35.1 ng/mL and 327 pg/mL, respectively (reference range: CEA < 5 ng/mL, calcitonin < 14 pg/mL). Urinary metanephrine and normetanephrine excretion were both elevated, at 1.3 mg/

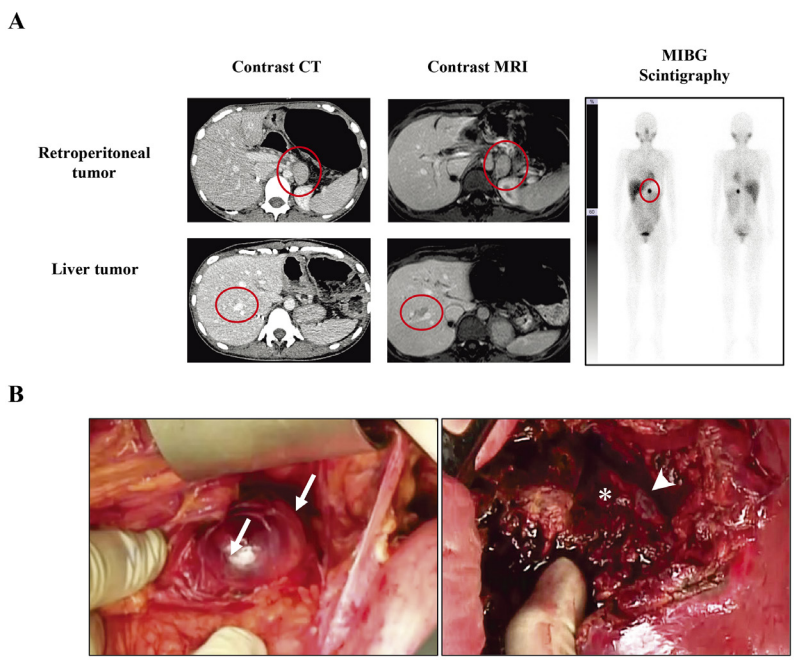

Fig. 1. Preoperative and intraoperative images.
(A) Enhanced computed tomography (CT) revealed a 30 mm-sized mass nearby the upper pole of the left kidney. A 16 mm low-density mass in the liver located in segment six was confirmed using enhanced magnetic resonance imaging (MRI). ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy showed an accumulation of isotopes in the tumor of the retroperitoneum. S6 segmentectomy was performed for the liver tumor. (B) A tumor with a well-defined border is observed in the retroperitoneum. White arrows represent the retroperitoneal tumor (left), the arrowhead represents the right hepatic vein (right), and the asterisk indicates the stump of the S6 Glisson (right).

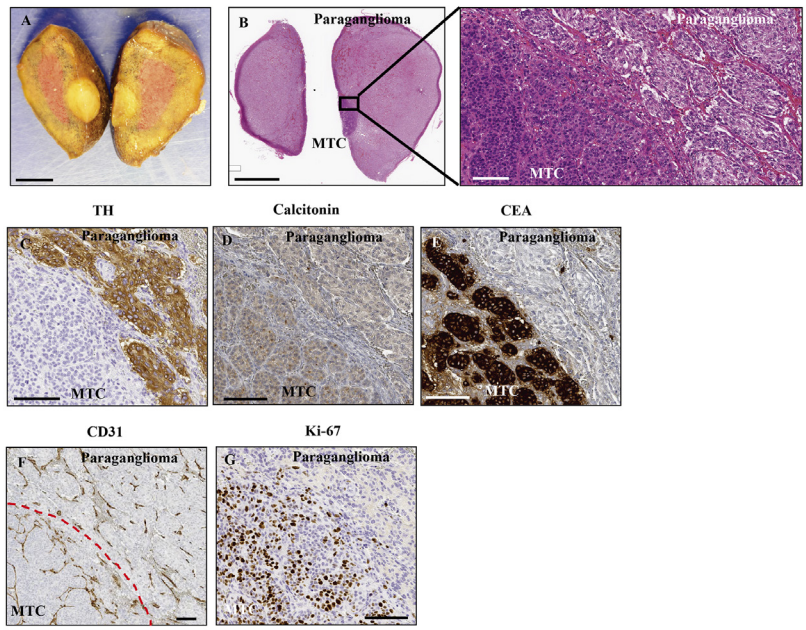

Fig. 2. Macro- and microscopic images of the retroperitoneal tumor.
(A) A gross image of the retroperitoneal tumor. The retroperitoneal tumor was yellow, solid, and had a smooth surface. The tumor showed the classic Zellballen pattern. An 8 mm well-circumscribed white nodule was observed inside the paraganglioma. (B) Atypical cells with large nuclear-to-cytoplasmic (N/C) ratio and dense nuclei proliferated and formed tubular structures [hematoxylin and eosin (HE) staining]. (C) The tumor was negative for tyrosine hydroxylase (TH), (D) weakly positive for calcitonin, and (E) positive for carcinoembryonic antigen (CEA). (F) There were no CD31-positive vessels around the tumor, and the intravascular invasion was also negative. (G) Ki-67 positive rate of paraganglioma was 11.6%, whereas that of medullary thyroid carcinoma (MTC) was 42.4%. Scale bars of A and B (left): 5 mm; scale bars of B (right), C, D, E, F, and G: 100 μm.

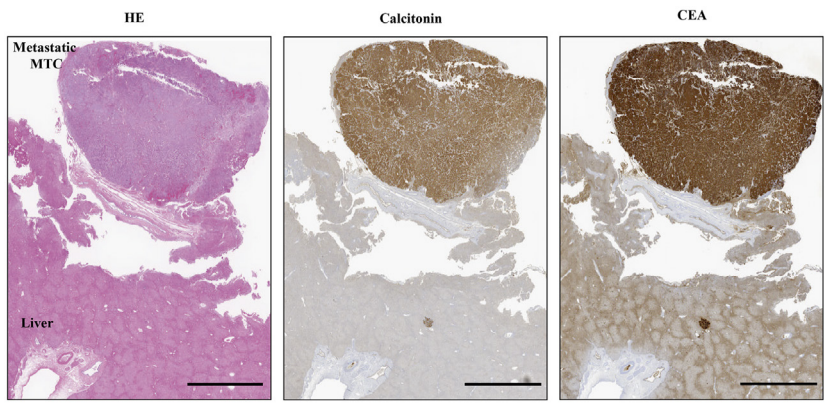

Fig. 3. Microscopic images of metastatic liver tumor.
The metastatic liver tumor was positive for calcitonin and carcinoembryonic antigen (CEA). Scale bars: 5 mm. HE, hematoxylin and eosin staining; MTC, medullary thyroid carcinoma.

day. Urinalysis also revealed the elevated excretion of vanillylmandelic acid and noradrenaline (9.1 mg/day and 211 μg/day, respectively; reference range: vanillylmandelic acid 1.5-4.9 ng/mL, noradrenaline < 120 μg/day). Based on these results, a local recurrence of pheochromocytoma was highly suspected. The hepatic low-intensity mass was also suspected to be a liver metastatic pheochromocytoma (Fig. 1A).

The retroperitoneal and hepatic tumors were resected. No dissemination or ascites was observed in the abdominal cavity. The tumor in the retroperitoneum had a well-defined border, and there was no invasion of the surrounding tissues (Fig. 1B). S6 segmentectomy was performed for the liver tumor (Fig. 1B). The retroperitoneal tumor was yellow, solid, with a smooth surface, and 30 mm in size (Fig. 2A). The classic Zellballen pattern, which is typical for pheochromocytoma (Turk et al. 2022), was observed, consisting of chief cells positive for chromogranin A and sustentacular cells positive for S-100 on immunopathological examination. Therefore, the patient was diagnosed with paragangli-

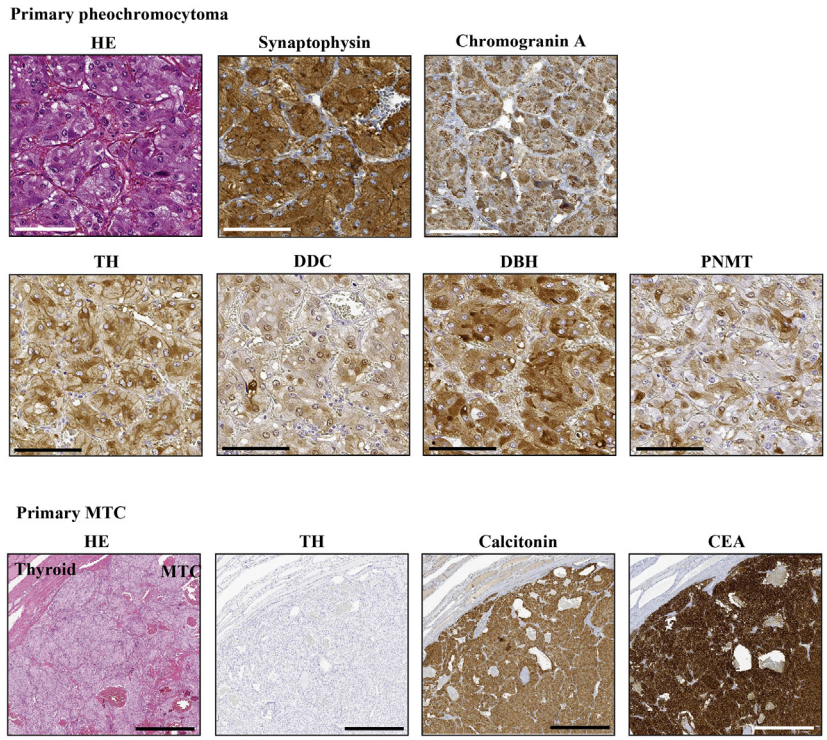

Fig. 4. Pathological findings of primary pheochromocytoma resected at the age of 29 and medullary thyroid carcinoma (MTC) resected at the age of 15.
The pheochromocytoma tested positive for synaptophysin, chromogranin A, TH, dopa decarboxylase (DDC), dopamine beta-hydroxylase (DBH), and phenylethanolamine N-methyltransferase (PNMT). Primary MTC was negative for tyrosine hydroxylase (TH) but positive for calcitonin and carcinoembryonic antigen (CEA). Scale bars in primary pheochromocytoma (uppear panels): 100 μm; scale bars in primary MTC (lower panels): 500 μm. HE, hematoxylin and eosin staining.

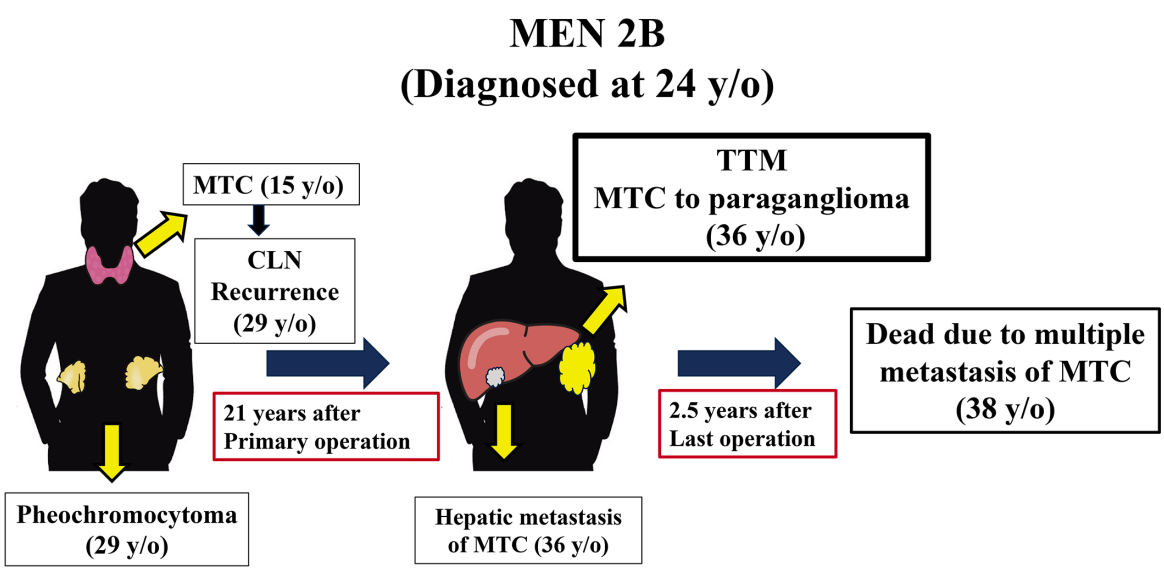

Fig. 5. Clinical events of the patient by the age.
CLN, cervical lymph node; MEN 2B, multiple endocrine neoplasia type 2B; MTC, medullary thyroid carcinoma; TTM, tumor to tumor metastasis; y/o, years old.

oma. A well-circumscribed white nodule was inside the paraganglioma (Fig. 2A), and atypical cells with large nuclear-to-cytoplasmic (N/C) ratio and dense nuclei were observed forming tubular structures (Fig. 2B). These cells were negative for tyrosine hydroxylase (TH) (Fig. 2C), which is a marker of catecholamine-containing neurons and endocrine cells (Tischler et al. 2014), weakly positive for calcitonin (Fig. 2D), positive for CEA (Fig. 2E), and nega-

Table 1. Reported cases of metastasis from thyroid carcinoma.

Number	Sex	Age	Type of thyroid carcinoma (Donor tumor)	Recipient tumor	Other metastasis	Transformation to aggressive characteristics	Reference
1	M	82	Papillary	Lung squamous cell carcinoma	CLN	N/A	Nonomura et al. 1994
2	F	44	Papillary	Lung adenocarcinoma	CLN	N/A	Kim et al. 2012
3	F	64	Papillary	Anaplastic meningioma	Bones and CLN	Sarcomatoid differentiaton	Das et al. 2017
4	M	72	Papillary	Renal cell carcinoma	CLN	N/A	Song et al. 2017
5	F	53	Papillary	Uterine leiomyoma	Bones and lungs	Poor tumor differentiation	Bertrand et al. 2019
6 (our case)	F	35	Medullary	Paraganglioma	Liver	Poor tumor differentiation	

CLN, cervical lymph node; F, female; M, male; N/A, not addressed.

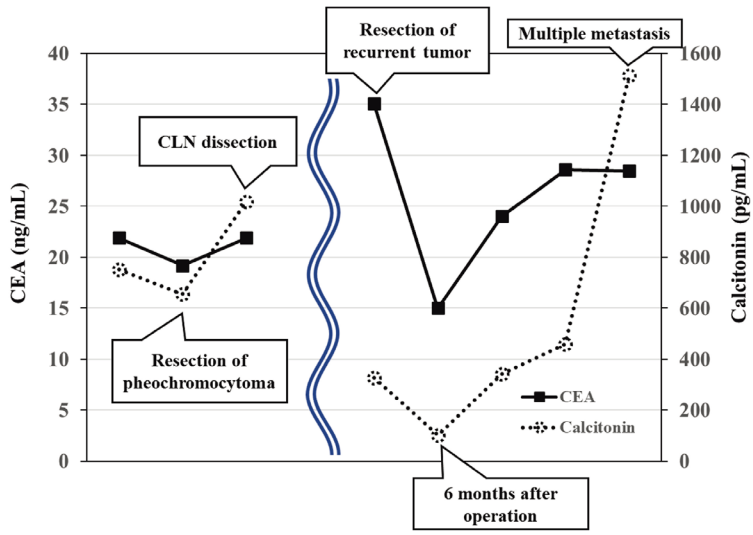

Fig. 6. Transition of carcinoembryonic antigen (CEA) and calcitonin.
CEA and calcitonin levels were elevated when medullary thyroid carcinoma (MTC) recurrence was confirmed. The levels of these markers decreased after MTC resection. CLN, cervical lymph node.

tive for chromogranin A, S-100 protein, and Ad4BP. The white nodule was not surrounded by vessels, and intravascular invasion was negative (Fig. 2F). Based on the immunohistopathological findings, the white nodule in the paraganglioma was diagnosed as a metastasis of MTC. The liver tumor was positive for calcitonin and CEA (Fig. 3) and negative for S-100 protein. Histopathological examination confirmed that the liver lesion was a metastasis of the MTC. The Ki-67 positive ratio of the liver tumor was 2.3%, whereas that of MTC in paragangliomas was 42.4% (Fig. 2G). The pathological findings of pheochromocytoma and MTC during the primary operation are shown in Fig. 4. Primary MTC was negative for TH and positive for calcitonin and CEA. However, metastatic MTC in paragangliomas was weakly positive for CEA, and its N/C ratio was higher than that of the primary tumor. The Ki-67 ratio was also high in metastatic MTC. MTC in paragangliomas became highly malignant and TTM occurred. The patient died 2.5 years after the last surgery because of multiple metastases of MTC to the liver, bone, and lungs. Clinical events of the patient by the age are shown in Fig. 5.

Discussion

This is the first report of TTM from MTC to paraganglioma, in a patient with MEN 2B. TTM was first reported and defined by Berent (1902). Four strict diagnostic criteria for TTM must be met: (i) more than one primary tumor must exist; (ii) the recipient tumor must be a true benign or malignant neoplasm; (iii) the metastatic neoplasm must be a true metastasis with established growth in the host tumor, not the result of contiguous growth (collision tumor) or embolization of donor tumor cells; and (iv) tumors that have metastasized to the lymphatic system should be excluded. In this case, the donor tumor was a recurrent MTC, and the recipient tumor was a paraganglioma. The donor tumor was located just inside the recipient tumor, and there was no vascular structure in the adjacencies. The border between the paraganglioma and MTC was clear, and no transition zone was observed. Therefore, the collision of the two tumors or embolization of the donor tumor was unlikely. In addition, the tumor did not contain lymphatic tissue so lymphatic spread was also unlikely. Based on these pathological findings, the patient met all the diagnos-

tic criteria, and a diagnosis of TTM was made. In addition, the TTM of the MTC occurred 20 years after the primary total thyroidectomy.

MTC in MEN 2B is aggressive and can disseminate to regional lymph nodes and distant organs, including the liver, lungs, and bones (Williams et al. 2008; Mandanas et al. 2015; Tanwar et al. 2018). Here, the operation was performed because there were no metastatic lesions other than those in the liver and retroperitoneum, which was confirmed through preoperative imaging examinations. Generally, donor tumors are more aggressive than recipient tumors in TTM. To the best of our knowledge, there have been 19 cases of TTM of thyroid carcinoma as a recipient tumor, most of which were papillary carcinomas (Yeo et al. 2014; Luo et al. 2020). Although colon cancer is reported to metastasize to MTC (Yeo et al. 2014), MTC was not documented as a donor tumor. There are only six reports of TTM in which the thyroid carcinoma metastasized to other tumors (Table 1). It is well known that papillary carcinomas likely to metastasize to the CLN and the CLN metastasis was observed in four out of five cases of papillary carcinomas with TTM (Bertrand et al. 2019). The tumors in three of these reports gained more aggressive characteristics compared with the primary tumors and metastasized to distant organs, including the bones, lungs, and liver, leading to a poor prognosis. Here, MTC in paragangliomas showed high Ki-67 positive and N/C ratios. This high malignant potential might have enabled MTC to metastasize to paragangliomas.

MTC cells secrete various serum markers, including CEA, calcitonin, and chromogranin A (Zarkesh et al. 2022). Calcitonin is a useful serum marker recommended in the guidelines for the preoperative diagnosis of MTC and postoperative monitoring of residual or recurrent disease (Thomas et al. 2019). More than 50% of the patients with MTC have an elevation of CEA (Busnardo et al. 1984). Calcitonin and CEA levels have high sensitivity and specificity in the preoperative diagnosis of patients with MTC and during postoperative follow-up (Han et al. 2021). In our case, the CEA and calcitonin levels were high during the follow-up period, and the elevation of these markers was observed when MTC recurrence occurred (Fig. 6). Marker levels also decreased after resection of recurrent MTC. Careful follow-up should be considered in such cases because MTC recurrence is a definitive prognostic factor in patients with MEN 2B. In cases that reported MTC recurrence to occur 15 years or decades after thyroidectomy, although there were no evident lesions on imaging, the calcitonin levels remained high (van Heerden et al. 1990; Williams et al. 2008).

In conclusion, this is the first report of TTM in a patient with MEN 2B, and MTC metastasized to the paraganglioma 20 years after the primary operation. In addition, MTC has acquired aggressive characteristics and metastasized as a donor tumor. Careful follow-up should be considered in cases with high CEA and calcitonin levels, even if it has been long since the first MTC operation.

Conflict of Interest

The authors declare no conflict of interest.

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