

# Pheochromocytoma arising from an ectopic adrenal tissue in multiple endocrine neoplasia type 2A

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## Summary

A 21-year-old woman was referred to our hospital to treat bilateral pheochromocytomas (PCCs) after a diagnosis of multiple endocrine neoplasia type 2A (MEN2A). We performed bilateral laparoscopic adrenalectomy. One year after the operation, urinary fractionated metanephrines in 24-h urine increased. MRI showed a 30 mm tumor on the interaortocaval region and <sup>123</sup>I-MIBG concentrated in this area. We excised the tumor and performed para-aortic lymphadenectomy. Histopathologic examination confirmed a PCC arising from ectopic adrenal tissue. Urinary fractionated metanephrines in 24-h urine declined to basal levels immediately after the operation. We detected no recurrence of paraganglioma or PCC for 5 years after the treatment.

## Learning points:

- Most ectopic adrenal tissue is associated with no symptoms and contains only the adrenal cortex.
- Adrenocortical tumors sometimes arise from ectopic adrenal tissues similarly to in the normal adrenal gland.
- PCC arising from ectopic adrenal tissue occurs infrequently.
- MEN2-related PCC is accompanied by adrenal medullary hyperplasia, which might be part of tumorigenesis.

## Background

Multiple endocrine neoplasia type 2A (MEN2A) is one of multiple endocrine tumors syndrome. All are caused by mutations in the rearranged during transfection (*RET*) gene and are inherited in an autosomal dominant fashion. Approximately 40–50% of patients with MEN2A develop pheochromocytoma (PCC) and 90% develop medullary thyroid carcinoma. PCCs are bilateral in more than 50% of cases but are usually benign. Therefore, partial adrenalectomy to preserve adrenal cortex function is accepted for patients with MEN2A who have bilateral PCCs (1).

Ectopic adrenal tissue is a condition that presents in adrenal tissue far from adrenal glands. It occurs in up to 50% of neonates. However, it is found in less than 1% of adults because ectopic adrenal tissue usually regresses in early infancy. Most ectopic adrenal tissue is asymptomatic

and found incidentally during operations such as inguinal hernia repair (2). However, ectopic adrenal tissue and malignant tumors can be difficult to distinguish if located in renal or hepatic parenchyma (3). Some case reports have described functional adrenocortical adenoma or adrenocortical carcinoma arising from ectopic adrenal tissue. However, no case report has shown that PCC arises from ectopic adrenal tissue. This report presents the first case of adrenal medulla tumor, PCC, arising from ectopic adrenal tissue in a patient with MEN2A.

## Case presentation

A 21-year-old Japanese woman who had been diagnosed with MEN2A presented with intermittent headaches

and palpitations. Her mother and grandmother were diagnosed as MEN2A too. An abdominal MRI showed bilateral adrenal tumors containing cystic lesions. Right side and left side tumors were 40 and 50 mm, respectively. The urinary fractionated metanephrine level in 24-h urine was 3.7 mg/day (normal: 0.05-0.23 mg/day).  $^{123}\text{I}$ -MIBG was concentrated in bilateral adrenal tumors and the patient was diagnosed with bilateral PCCs. We performed bilateral laparoscopic adrenalectomy simultaneously. We orally administered  $\alpha$ -adrenergic receptor blockers before the operation. We did not perform partial adrenalectomy to preserve adrenal cortex functions because the tumors' cystic walls were thin. She received permanent replacement therapy with hydrocortisone after the first operation. Pathological diagnosis was bilateral PCCs; the Ki67 index was below 2%. Three months after the bilateral adrenalectomy, she received prophylactic total thyroidectomy.

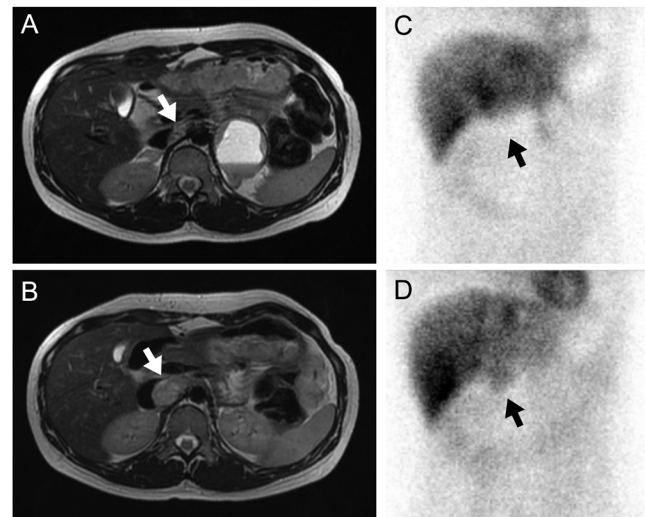
Five and 12 months after the first operation, the urinary fractionated metanephrine level in 24-h urine were 0.32 mg/day and 0.44 mg/day respectively. We could not detect any apparent tumor in abdominal MRI before the first operation (Fig. 1A), but abdominal MRI 12 months after the bilateral adrenalectomy showed a 30 mm tumor on the interaortocaval region around the hilum of the kidney (Fig. 1B). Additionally,  $^{123}\text{I}$ -MIBG newly concentrated in the tumor (Fig. 1C and D).

### Investigation and treatment

We performed PET-CT to ascertain whether another tumor existed. PET-CT concentrated on the same area and revealed no new lesions there. Given these findings, we suspected paraganglioma or malignant PCC, so we performed tumor excision and lymph node dissection around the abdominal aorta. The tumor lay between the vena cava and aorta under the left renal vein, and was completely resected without capsule injury. The resecting tumor contained a yellowish small lesion (Fig. 2A). Histological findings showed that the adrenal cortex and capsule existed in the tumor's outer layer (Fig. 2B). Immunohistochemistry with chromogranin indicated that the tumor was PCC (Fig. 2C). The Ki67 index was 3-4%. No tumor was found in resected lymph nodes. The final diagnosis was PCC arising from ectopic adrenal tissue.

### Outcome and follow-up

Three months after tumor excision, the urinary fractionated metanephrine level in 24-h urine was



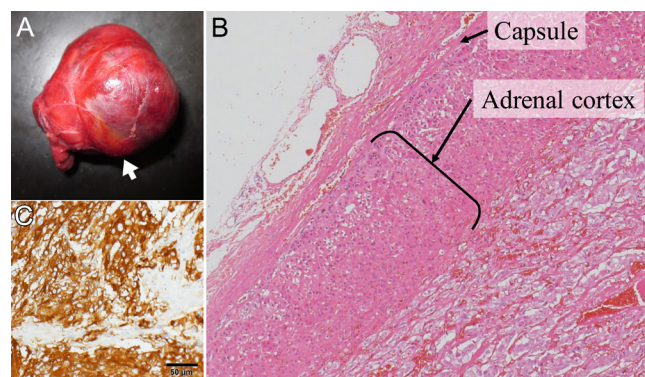
**Figure 1**

(A) White arrow shows the same lesion in abdominal MRI T2WI 1 year previously, but an apparent tumor is not detected. (B) White arrow shows a 30-mm tumor on the interaortocaval region in abdominal MRI T2WI. (C) Black arrow shows the same lesion one year previously, but an apparent tumor concentrating  $^{123}\text{I}$ -MIBG is not detected. Focus is on bilateral PCCs. (D) Black arrow shows a tumor concentrating  $^{123}\text{I}$ -MIBG.

0.01 mg/day.  $^{123}\text{I}$ -MIBG was not concentrated in her body. We have detected no recurrence or metastasis of PCC and paraganglioma for 5 years after the operation.

### Discussion

Also known as extra-adrenal PCC, paraganglioma is a tumor derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen, and pelvis. Pheochromocytoma in MEN2 is usually located in the adrenal medulla, but paraganglioma occurs



**Figure 2**

(A) White arrow shows a yellowish small lesion of the tumor, which indicates that it is the adrenal cortex. (B) The adrenal cortex and capsule are present in an outer layer of the tumor. (C) Chromogranin is positive in the tumor.



in 3% of patients with MEN2 (4). In our case, PCC arose from ectopic adrenal tissue and contained adrenal cortex. Therefore, it was distinct from paraganglioma. Some case reports indicate that functional adrenocortical adenoma, such as Cushing syndrome (5) or primary aldosteronism (6), arise in ectopic adrenal tissue similarly to normal adrenal glands. Herein, we report the first case of PCC arising from ectopic adrenal tissue.

Adrenal gland organogenesis derives from the adrenal primordium originating from the mesoderm and neural crest originating from the ectoderm. The adrenal-gonadal primordium arising from the mesoderm separates into adrenal primordium and gonadal primordium in the eighth week of gestation in humans. After that, neural crest cells migrate into the adrenal primordium, also known as the fetal cortex, and form adrenal medulla. Formation of a mesenchymal capsule around the adrenal primordium subsequently occurs (7).

The adrenal gland is usually located above the kidney. Ectopic adrenal tissue is caused by aberrant adrenal gland organogenesis. Because the adrenal primordium is separated from the adrenal-gonadal primordium, areas involved in the gonad such as the spermatic cord are frequent sites of ectopic adrenal tissue. Some reports show that ectopic adrenal tissue is observed in inguinal hernia surgeries (2) and in resected ovarian tumors (8). These reports indicate that ectopic adrenal tissue usually contains only the adrenal cortex and is found accidentally. Additionally, organs originating from the mesoderm, such as the kidney and liver, are also frequent sites of ectopic adrenal tissue (3). In these cases, it is difficult to distinguish malignant tumors arising from these organs from ectopic adrenal tissue without histological assessment, and ectopic adrenal tissue contains only the adrenal cortex (3). These findings suggest that most ectopic adrenal tissues are caused by aberrant separation of the adrenal-gonadal primordium or mesoderm before migration of neural crest cells. The adrenal medulla is sometimes observed when ectopic adrenal tissue is in near the original site of the adrenal gland (9). In these cases, aberrant separation occurs in partially matured adrenal glands after migration of neural crest cells. Our patient's ectopic adrenal tissue contained PCC, which arose from around the original site of her adrenal gland in agreement with the above explanation.

Multiple endocrine neoplasia type 2A is a multiple endocrine neoplasia syndrome caused by germline activating *RET* proto-oncogene mutations and characterized by medullary thyroid cancer and PCC (1). Approximately 50% of patients with the *RET* mutation

develop PCC. Furthermore, more than 50% of patients with MEN2-related PCC suffer from this bilaterally. Fortunately, malignancy is rare (0–4.1%). Therefore, adrenal-sparing surgery is a good option for patients with MEN2A, and has been performed successfully (1). On the one hand, some patients with MEN2A present with adrenal medullary hyperplasia. Similar molecular aberrations were found in both adrenal medullary hyperplasia and PCC (10). In our case, a structure smaller than 10mm in width, which appeared to be ectopic adrenal medullary hyperplasia, developed into PCC one year later. The adrenal medulla can be contained in ectopic adrenal tissue and MEN2-related PCC arises in the context of adrenal medullary hyperplasia. Permanent PCC follow-up is needed for patients with MEN2A, even if they receive complete adrenalectomy.

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#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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#### Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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#### Author contribution statement

H O conceived and drafted this manuscript. N T and H K reviewed and revised this manuscript prior to submission. T M provided the final approval for this manuscript for publication. He is also the corresponding author. All authors read and approved the final manuscript.

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