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Adrenal Corticomedullary Mixed Tumor Associated With the *FGFR4*-G388R Variant

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Adrenal corticomedullary mixed tumors (CMMTs) are extremely rare; with only 20 cases being reported to date, the pathogenesis has remained elusive. A 31-year-old woman developed gestational hypertension with psychiatric disturbances persistent to postpartum and was diagnosed with pheochromocytoma, for which adrenalectomy was performed. Histological findings showed mixed adrenocortical adenoma and pheochromocytoma. Double immunostaining of inhibin and INSM1 (insulinoma-associated protein 1) showed that the 2 tumor components had distinct functional properties. Exome analysis of peripheral leukocytes and tumor (singular, as anatomically it is only 1 mass) revealed a homozygous germline *FGFR4*-G388R variant. As a readout of the variant, serine phosphorylation of signal transducer and activator of transcription 3 (STAT3) was detected only in the nucleus of adrenocortical adenoma component but not in the pheochromocytoma component. No tyrosine phosphorylation of STAT3 was detected. We report a case of CMMT with the germline *FGFR4*-G388R variant. Although additional studies are required, our immunohistochemical analysis suggests that the variant may play a role in the development of the adrenocortical component within the pheochromocytoma, leading to CMMT.

Key Words: adrenal gland, corticomedullary mixed tumor, FGFR4-G388R variant

Adrenocortical adenomas and pheochromocytomas are representative adrenal tumors, originating from the adrenal cortex and medulla, respectively. In rare cases, pheochromocytoma secretes adrenocorticotropin (ACTH), resulting in Cushing's syndrome, highlighting the fact that pheochromocytoma belongs to the class of neuroendocrine tumors. However, a single adrenal tumor showing coexistence of adrenocortical adenoma and pheochromocytoma is considerably rare and is known as a corticomedullary

Abbreviations: 3β-HSD, 3β-hydroxy-Δ5-steroid dehydrogenase; ACTH, adrenocorticotropic hormone; CMMT, corticomedullary mixed tumor; CT, computed tomography; CYP11β, cytochrome P450 family 11 subfamily β; CYP17, 17α-hydroxyl/17,20-lyase; DBH, dopamine beta hydroxylase; MIBG, metaiodobenzylguanidine; INSM1, insulinoma-associated protein 1; PNMT, phenylethanolamine-N-methyl transferase; p-S727 STAT3, phosphoserine-727 STAT3; p-Y705 STAT3, phosphotyrosine-705 STAT3; SF-1, steroidogenic factor 1; STAT3, signal transducer and activator of transcription 3; TH, tyrosine hydroxylase; UFC, urine free cortisol.

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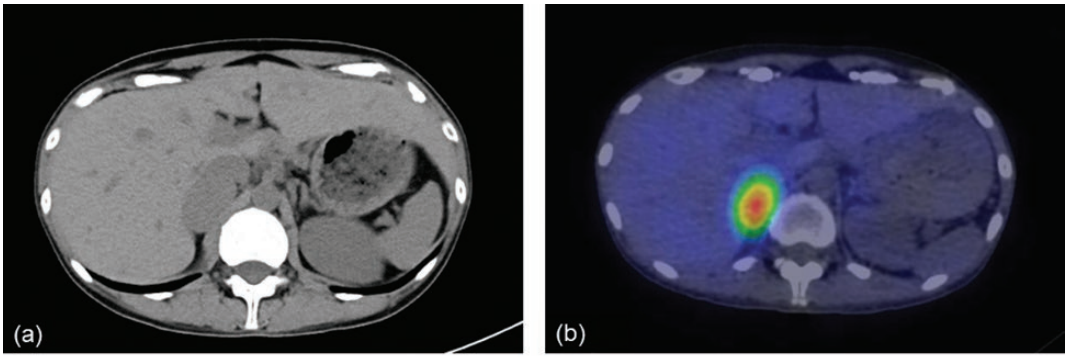
mixed tumor (CMMT). To date, only 20 cases of CMMT have been reported [1-5]. These cases have shown female predominance (76%), autonomous cortisol-secretion (40%), and histologic malignancy (10%) [1-5]. The pathogenesis of CMMT remains largely unclear. Although various pathogenic gene alterations in adrenocortical adenomas and pheochromocytomas have been reported, there have been no genes shared between them [6, 7]. Herein, we report a case of CMMT, for which exome sequencing and immunohistochemical analysis were performed to provide evidence for potential mechanisms underlying the pathogenesis.

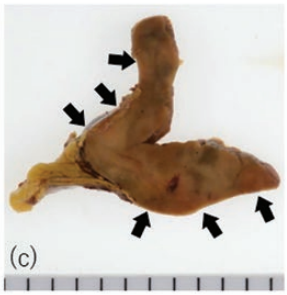
Case Description

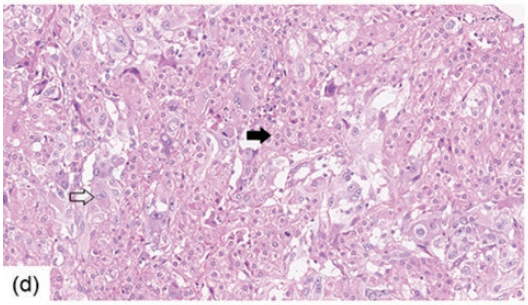
A 31-year-old woman was referred to our hospital because of hypertension at 14 weeks of gestation. She had no notable medical or family history. Physical examination revealed no apparent signs of Cushing's syndrome. Due to gestational hypertension, administration of antihypertensive drugs was initiated. At 27 weeks of gestation, she experienced panic disorder, emotional incontinence, and hyperpnea attacks. At 29 weeks, emergency cesarean section was performed due to uncontrollable hypertension (214/140 mmHg). However, severe hypertension persisted after delivery. Endocrinological examination revealed elevated plasma catecholamine levels (Table 1). Abdominal computed tomography (CT) showed a 38 × 24 mm mass in the right adrenal gland (Fig. 1a), which exhibited ^{123}I-meta-iodobenzylguanidine (MIBG) uptake (Fig. 1b). At this point, we had not anticipated the possibility of Cushing's syndrome, since she had few signs of Cushing's or disorder of the hypothalamic-pituitary-adrenal (HPA) axis during pregnancy, despite high urine free cortisol (UFC) levels. Therefore, a dexamethasone suppression test was not performed. Based on these results, the patient was diagnosed with pheochromocytoma, and subsequent laparoscopic tumor resection was performed 1.5 months after delivery. After tumor resection, serum cortisol level and UFC excretion substantially decreased, accompanied by an increase in plasma ACTH levels, suggesting that the tumor produced cortisol (Table 1). The resected tumor was solid and tan-colored, without hemorrhage or necrosis (Fig. 1c). Histologically, the tumor consisted of 2 components of irregularly mixed cells. (Fig. 1d). One displayed oxyphilic cytoplasm with large nuclei, which was regarded as a pheochromocytoma. The other had eosinophilic cytoplasm with small rounded nuclei, which was regarded as an adrenocortical adenoma. The pheochromocytoma component accounted for 60% of the whole tumor. Postoperatively, her blood pressure and mental status normalized, with normal serum catecholamine levels. No tumor recurrence or metastases have been detected in the 3 years since surgery.

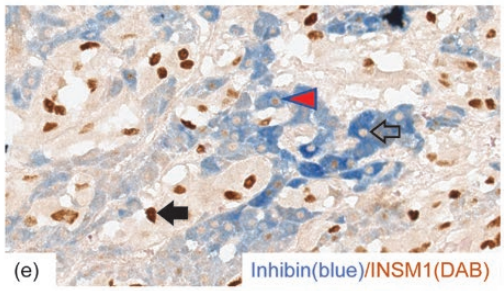
Table 1. Endocrinological Findings

		Pregnant (29 weeks)	Postpartum (1 month)	Postoperation (3 months)	Postoperation (21 months)	Reference range
Plasma levels						
Noradrenaline	(ng/mL)	2.1	1.5	0.14	0.32	0-0.17
Adrenaline	(ng/mL)	2.1	1.1	<0.01	<0.01	0.15-0.57
Dopamine	(ng/mL)	0.21	0.13	<0.02	<0.02	0-0.03
ACTH	(pg/mL)	29.5	9.6	28.1	35.6	7.7–63.1
Serum level						
Cortisol	(μg/dL)	29.7	16.6	5.6	5.8	5.9-17.0
Urine metabolites						
Normetanephrine	(mg/day)	3.6	1.2	0.12		0.05-0.3
Metanephrine	(mg/day)	1	5.9	0.18		0.05-0.2
Free cortisol	(μg/day)		214.6	17.8		11.2-80.3









	NOC (%)
inhibin(+)/INSM1(-)	136 (45.3)
inhibin(-)/INSM1(+)	158 (52.6)
inhibin(+)/INSM1(+)	6 (2.1)
total	300 (100)

NOC, number of cells

(f)

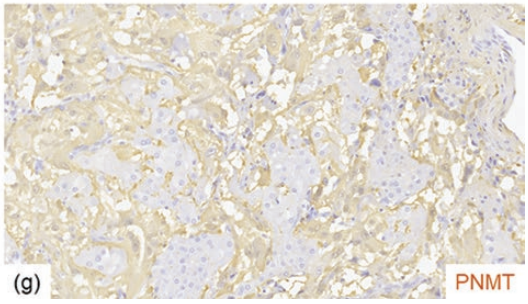


Figure 1. Imaging and immunohistochemical analysis (a) Abdominal computed tomography. **(b)** ^{123}I-MIBG scintigraphy. **(c)** Gross pathological findings of CMMT (arrows). **(d)** Hematoxylin and eosin staining of the CMMT; pheochromocytoma (oxyphilic large cytoplasm with large nuclei; open arrow) and adrenocortical adenoma (eosinophilic cytoplasm with small rounded nuclei; closed arrow). Immunohistochemical findings of CMMT. **(e)** Inhibin was cytoplasmic positive for adrenocortical adenoma (open arrow), and insulinoma-associated protein 1 (INSM1) was nuclear positive for pheochromocytoma (closed arrow), mainly separately. Few double positive cells were identified (red arrowhead). **(f)** Quantitative analysis of inhibin/INSM1 staining. **(g)** Phenylethanolamine-N-methyl transferase (PNMT), **(h)** dopamine beta hydroxylase (DBH), and **(i)** tyrosine hydroxylase (TH) were positive only in the pheochromocytoma component. **(j)** Steroidogenic factor 1 (SF-1), **(k)** 3β-hydroxy-Δ5-steroid dehydrogenase (3β-HSD), and **(l)** 17α-hydroxyl/17,20-lyase (CYP17) were positive for adrenocortical adenoma components. **(m)** Cytochrome P450 family 11 subfamily β-member 1 (CYP11β1) was positive in the adrenocortical adenoma component, whereas **(n)** CYP11β2 was negative. **(o)** ACTH was negative. **(p)** Ki-67 labeling index was less than 1%.

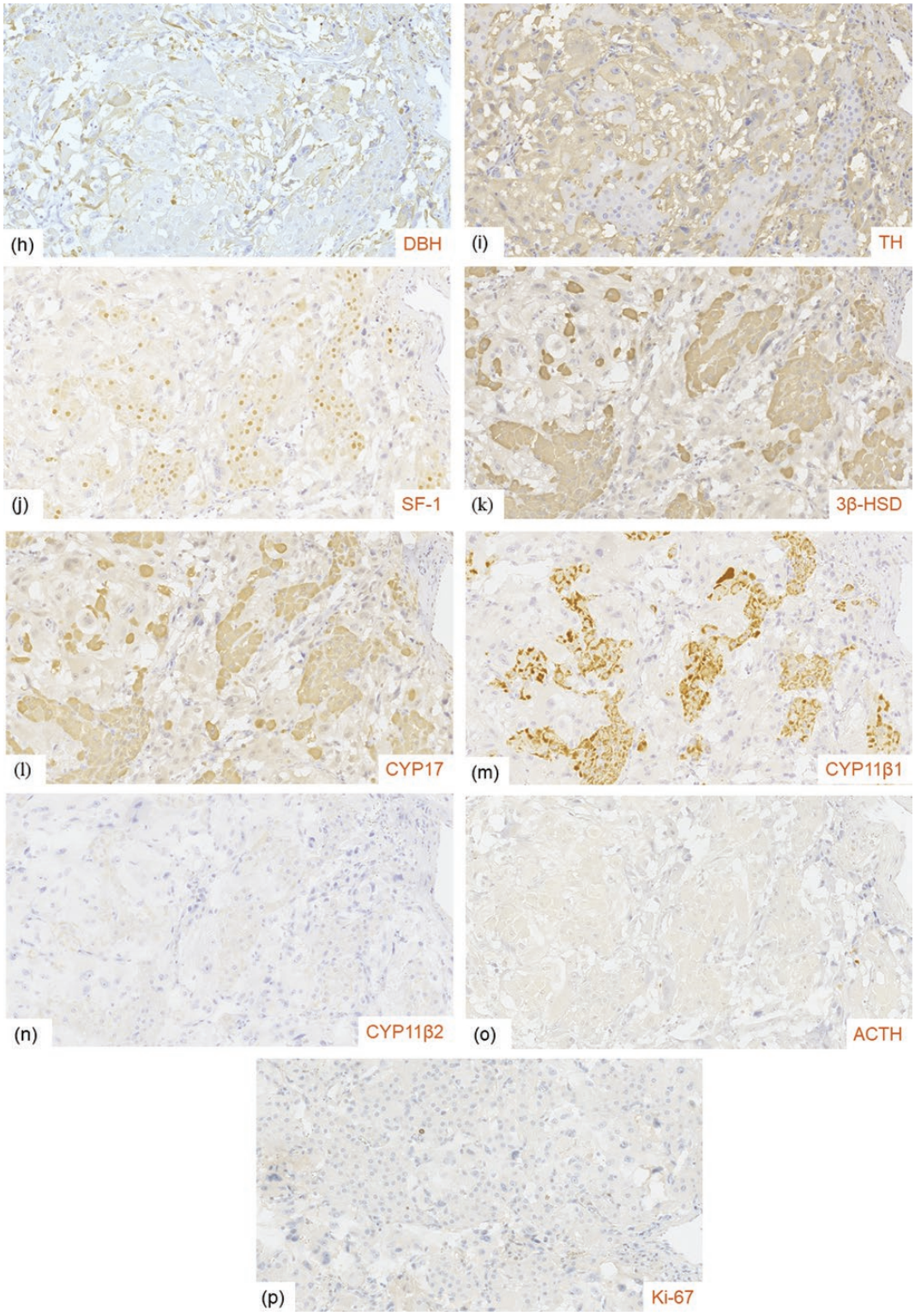


Figure 1. Continued.

Immunohistochemical Analysis

Double immunostaining revealed that the pheochromocytoma component was nuclear positive for insulinoma-associated protein 1 (INSM1), a neuroendocrine transcriptional marker,

and the adrenocortical adenoma component was cytoplasmic positive for inhibin, a marker of steroid-producing cells (Fig. 1e). We evaluated a total of 300 cells in 4 different high power field views, which identified 136 inhibin (+) / INSM1 (−) cells, 158 inhibin (−) / INSM1 (+) cells, and 6 inhibin (+) / INSM1 (+) cells (Fig. 1e and f). Although few cells showed double positivity, positive intensity was weaker than that of single INSM1-positive cells.

The pheochromocytoma component was positive for synaptophysin, chromogranin A, and catecholamine synthesis enzymes, such as tyrosine hydroxylase (TH), dopamine beta hydroxylase (DBH), and phenylethanolamine-N-methyl transferase (PNMT) (Fig. 1g-i). The adrenocortical adenoma component was positive for steroidogenic factor 1 (SF-1) (Fig. 1j) and steroid hormone synthesis enzymes, such as 3β-hydroxy-Δ5-steroid dehydrogenase (3β-HSD) and 17α-hydroxyl/17,20-lyase (CYP17) (Fig. 1k, l). Moreover, cytochrome P450 family 11 subfamily β-member 1 (CYP11β1) was positive, while CYP11β2 was negative (Fig. 1m and 1n), suggesting cortisol production in these cells. Although we could not verify that the patient had Cushing's syndrome during the diagnostic process, endocrinological findings at postpartum (Table 1) exhibited relatively low plasma ACTH levels with normal serum cortisol levels, and elevated UFC levels, suggesting autonomous cortisol hypersecretion. Moreover, both serum cortisol and UFC levels decreased after surgery with restoring ACTH levels, supporting the diagnosis of subclinical Cushing's syndrome. Immunostaining exhibited that ACTH was negative in the pheochromocytoma component (Fig. 1o), indicating no ectopic ACTH production. The Ki-67 labeling index was less than 1% (Fig. 1p). On the basis of the histological findings, we diagnosed the patient with CMMT. The primary antibodies against INSM1 (1:50, Santa Cruz Biotechnology, California [8]), inhibin (1:000, Dako, Glostrup, Denmark [9]), synaptophysin (Roche Diagnostics, Mannheim Germany [10]), chromogranin A (1:200, Dako [11]), TH (1:2000, Sigma-Aldrich Milan, Italy [12]), DBH (1:1000, Abcam, Cambridge, MA [13]), PNMT (1:2000, Abcam, Cambridge, MA [14]), SF-1 (1:10, Thermo scientific, Cheshire, UK [15]), 3β-HSD (1:200, Santa Cruz Biotechnology [16]), ACTH (1:1000, Dako [17]), ki-67 (1:5, Dako [18]) were used. CYP17 antibody was developed in-house and its design and validation has been previously reported [19]. Rat monoclonal antibody for CYP11β1, and mouse monoclonal antibody for CYP11β2 were developed in the laboratory of Dr. Gomez Sanchez (University of Mississippi Medical Center, Jackson, MS) [20-22].

Whole Exome Sequencing Analysis

Whole exome sequencing analysis was performed using genomic DNA extracted from the peripheral leukocytes and tumoral paraffin-embedded tissue using a QIAamp DNA FFPE kit (QIAGEN Inc., Hilden, Germany), following the manufacturer's instructions. Variant analysis and interpretation were performed using the Opal Clinical interface (Fabric Genomics, CA), which employs proprietary algorithms to prioritize candidate variants by integrating phenotypic and genomic data. All experiments were conducted in compliance with the protocol that was reviewed and approved by the Research Ethics Committee of Kobe University Hospital (Permit Number: #1351). We obtained the patient's written informed consent.

Exome analysis revealed no germline or somatic gene alterations such as in *PRKACA*, *CTNNB1*, *GNAS*, *ARMC5*, *PRKAR1A*, *PDE11A*, or *PDE8B*, which have been reported in adrenal cortisol-producing adenomas, or in genes that have been reported in pheochromocytoma, such as *NF1*, *RET*, *VHL*, *SDHx*, *TMEM127*, *MAX*, *HIF2A*, *PHD1*/*PHD2*, *FH*, *KIF1B*, *DNMT3A*, *IDH1*, or *SLC25A11*. Although several germline heterozygous variants were detected in the genes related to pheochromocytoma, including *MDH2* p.Ala9Val, *KIF1B* p.Tyr1087Cys, *SDHAF1* p.Cys90Ser, *EPAS1* p.Thr766Pro, and *EGLN1* p.Cys127Ser, all of them were considered nonpathogenic polymorphisms according to the ClinVar classification. Loss of heterozygosity analysis also revealed no candidate genes. However, 10 genes were detected as possible pathogenic candidates using Opal algorithms, including some with amino acid substitution in the coding region, and as possible pathogenic variants by ClinVar classification, namely complement component 9 (*C9*), gap junction protein beta 2 (*GJB2*), phospholipase A2, group VII (*PLA2G7*), kallikrein B 1 (*KLKB1*), fibroblast growth

factor receptor 4 (*FGFR4*), solute carrier family 6, member 19 (*SLC6A19*), storkhead box1 (*STOX1*), and mannose binding soluble 2 (*MBL2*). Among these genes, we focused on the *FGFR4* variant as the most likely candidate associated with tumorigenesis. The results of the germline homozygous *FGFR4 c.1162G>A,* (p.G388R) variant was confirmed by Sanger sequencing (Fig. 2a).

Association of *FGFR4*-G388R With CMMT

It has been reported that the variant *FGFR4*-G388R is associated with the promotion of several tumors mainly by enhancing STAT3 signaling [23]. In pituitary adenomas with *FGFR4*-G388R, phosphorylation of STAT3 at the serine residue instead of the tyrosine residue has been shown to play a pivotal role in the pathogenesis [24]. To elucidate the role of the *FGFR4*-G388R variant in CMMT, we investigated STAT3 phosphorylation status in the CMMT specimens by immunohistochemistry using phosphoserine (p-S)727 STAT3 (1:200, Cell Signaling Technology [25]), and phosphotyrosine (p-Y)705 STAT3 (1:200, Cell Signaling Technology [26]) antibodies. Interestingly, most of the p-S727 STAT3 nuclear positive cells seemed to be adrenocortical adenoma cells (Fig. 2b and c). In contrast, tyrosine phosphorylation of STAT3 was not detected in any part of the tumor specimens. Double immunostaining for p-S727 STAT3 (red) and inhibin (blue) revealed more clear positivity for p-S727 STAT3 in adrenocortical cells, which showed double positivity (Fig. 2d). We evaluated a total of 525 cells in 3 different views in high power field, which revealed that almost all p-S727 STAT3–positive cells also showed inhibin positivity (268/270, 99%), indicating that most of p-S727 STAT3–positive cells had adrenocortical features. Very few cells showed single positivity; 2 cells of p-S727 STAT3 (+) / inhibin (−), and 5 cells of p-S727 STAT3 (−) / inhibin (+) (Fig. 2e) were identified. As a control, we investigated other general cortisol-producing adrenocortical adenomas (n = 3) and pheochromocytomas (n = 3) showing negative staining for both p-S727 and p-Y705 STAT3, suggesting that the serine-phosphorylation of STAT3 in the CMMT was specific (Fig. 2f and 2g).

Discussion

In the present study, we report a case of CMMT exhibiting gestational hypertension. Immunohistochemical analysis showed that each component, namely adrenocortical adenoma and pheochromocytoma, were functionally separated but intermingled. A germline homozygous *FGFR4*-G388R variant was identified, and this variant may play a role in the development of this tumor.

Previous immunohistochemical studies, using neuroendocrine (chromogranin A and synaptophysin) and adrenocortical cell markers (inhibin, melan A, calretinin, and SF-1), have shown that CMMTs are composed of a mixture of 2 cell types; however, the functional properties of these components have not been demonstrated. In this study, we first showed the functional properties of adrenaline- and cortisol-producing cells, using catecholamine- (TH, DBH, and PNMT) and steroid-synthesis enzyme (3β-HSD, CYP17, and CYP11β1) staining. Furthermore, double immunostaining of markers for neuroendocrine and adrenocortical cells revealed that most of these cell components (97.9%) were separated. However, we also found that exceedingly small number of cells (2.1%) were double-stained (inhibin and INSM1). These double-positive cells showed very weak INSM1 staining compared with INSM1-positive/inhibin-negative cells, suggesting these cells seem to have different character from single-positive cells. Further investigation is needed whether these biphasic components are a specific feature of mixed tumor, including the trans-differentiation from adrenal medulla to cortex. Stress has been shown to induce trans-differentiation between adrenal medulla and cortex using lineage tracing mouse model [27], suggesting the possibility of this hypothesis. Although only a few previous studies have examined the tumorigenesis of CMMT, several hypotheses have been proposed. For example, it has been

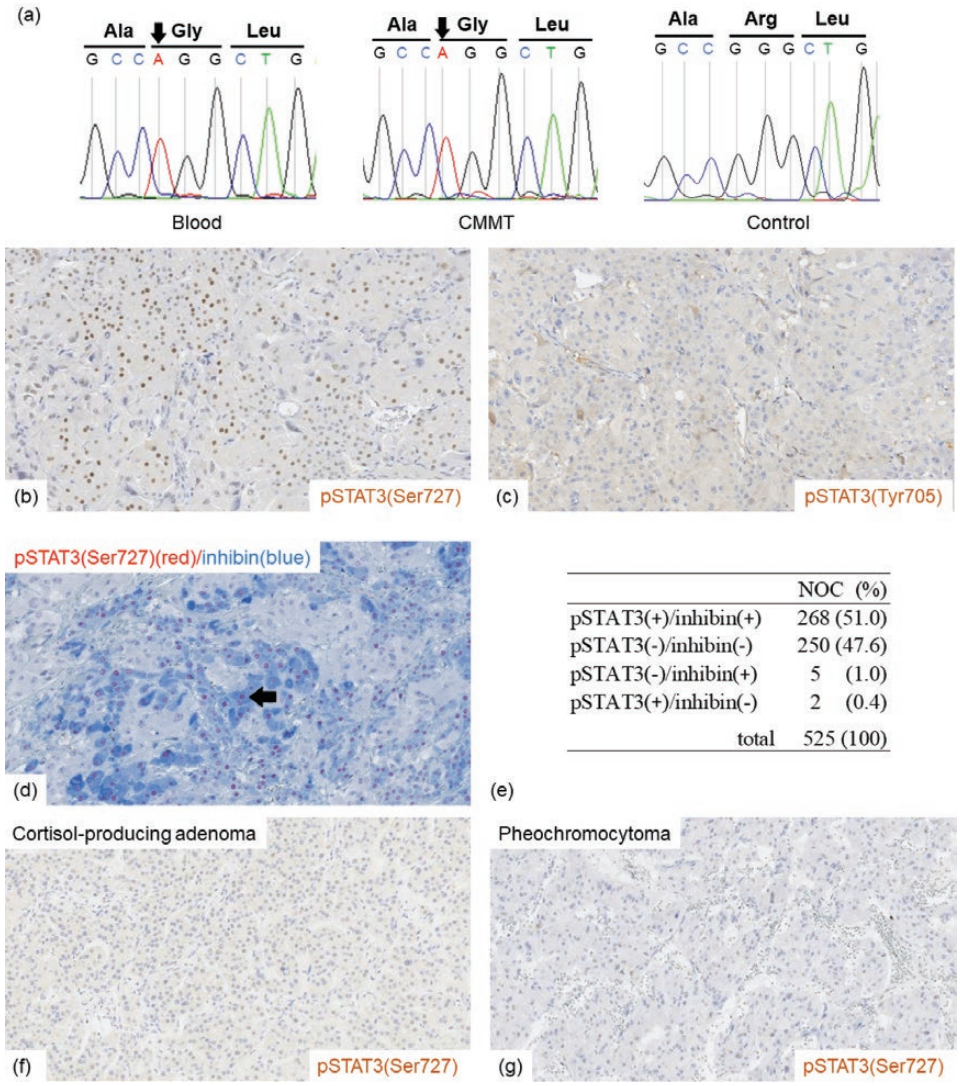


Figure 2. The results of sequencing analysis in *FGFR4* gene and immunostaining of phosphorylated STAT3 in CMMT (a) The results of Sanger sequencing analysis of the *FGFR4* gene using DNA from the patient's leukocytes, CMMT, and control leukocytes. **(b)** p-S727 STAT3 was positive in the nucleus only in the adrenocortical adenoma component. **(c)** p-Y705 STAT3 was negative in both the components. **(d)** p-S727 STAT3 (red) / inhibin (blue) double immunostaining. Most of nuclear p-S727 STAT3 (red) positive cells show cytoplasmic inhibin positive (arrow). **(e)** Quantitative analysis of inhibin/p-S727 STAT3 staining. **(f)** Other cortisol-producing adrenocortical adenomas and **(g)** pheochromocytomas showed negative staining for both p-S727 and p-Y705 STAT3. Representative data from each 3 cases are shown.

hypothesized that ACTH or growth factors derived from pheochromocytoma components might cause ectopic adrenocortical neoplasia [28]. In the present case, ACTH expression was not detected in pheochromocytoma cells. In addition to the ectopic ACTH production, catecholamine hypersecretion may induce pituitary ACTH secretion, which may lead to adrenocortical cell progression in pheochromocytoma [29]; however, this hypothesis cannot explain the condition in most pheochromocytomas. Furthermore, during pregnancy, the placenta is a source of ACTH and CRH, which exaggerates the circulating ACTH levels synergistically with ACTH induced by hyper catecholamine and may result in the proliferation of the cortical components within the pheochromocytomas. Another hypothesis is that tumor stem cells may contribute to the development of these 2 distinct tumor cells [5]. In the current study, whole exome analysis revealed the *FGFR4*-G388R variant as a possible

pathogenic gene alteration, and p-S727 STAT3, a downstream signal of the *FGFR4*-G388R variant, was observed mainly in the adrenocortical adenoma component, suggesting that the *FGFR4*-G388R variant and downstream signaling may play a role in the development of adrenocortical adenoma components. The result that p-S727 STAT3 was not detected in other general adrenocortical adenomas suggests this interesting hypothesis for the pathogenesis of CMMT.

Germline homozygous *FGFR4*-G388R has reportedly been associated with a poor prognosis and disease progression in several neoplasms, including breast, colon, prostate, skin, lung, head and neck, sarcoma, and endocrine tumors [23, 24]. Although in the previous 20 case reports on CMMT no genetic analysis has been reported, one case had a complicated breast cancer history [30]. It is tempting to speculate, that the patient in this case might have harbored the *FGFR4*-G388R variant.

One of the key downstream signaling pathways of the *FGFR4*-G388R variant is the STAT3 pathway [23, 24]. Canonical STAT3 activation is mediated by tyrosine phosphorylation, resulting in nuclear translocation. However, in pituitary adenoma with the *FGFR4*-G388R variant, the serine residue, instead of tyrosine, was phosphorylated, leading to the excess secretion of hormone and tumor progression [24]. In addition, it has been reported that p-S727 STAT3 plays an oncogenic role in several cancers, such as gastric cancer and glioma. Furthermore, ACTH-dependent p-S727 STAT3 activation has been associated with cell proliferation [31]. These data might support that the *FGFR4*-G388R variant and activation of STAT3 by serine phosphorylation play a pivotal role also in adrenocortical component tumorigenesis.

In pituitary adenomas with the *FGFR4*-G388R variant, p-S727 STAT3 was observed in mitochondrial localization [24]. In contrast, nuclear localization of p-S727 STAT was observed in gastric cancer and glioma. In our case, p-S727 STAT3 was located in the nucleus. Additional studies are needed to clarify the significance of the nuclear localization of p-S727 STAT3 in CMMT. Interestingly, p-S727 STAT3 was mostly observed in the adrenocortical adenoma component. The reason for this extremely high selectivity of p-S727 STAT3 in the cortical adenoma component is unclear. We speculate this may be related to ACTH. ACTH can selectively induce adrenocortical cell proliferation via the MC2R receptor. ACTH also has been shown to induce cell proliferation via the phosphorylation of p-S727 STAT3 [31]. In our patient, circulating ACTH levels were relatively elevated due to pheochromocytoma in addition to pregnancy. However, it cannot be excluded that the pathogenesis of the pheochromocytoma component may also be affected by the variant. Our hypothesis for the pathogenesis of CMMT is that pheochromocytoma first developed in an *FGFR4-G388R*–dependent or independent manner that at least did not involve STAT3. Subsequently adrenocortical trans-differentiation might have occurred through the activation of the serine phosphorylation of STAT3 because of the *FGFR4*-G388R variant. Although the reason of the lack of STAT3 activation in the pheochromocytoma component is not clear, its high selectivity to the adrenocortical adenoma component may likely to give a considerable hint for CMMT tumorigenesis.

In conclusion, we present a case of CMMT manifesting gestational hypertension and severe psychiatric disturbances, which has the germline *FGFR4*-G388R variant. Although further studies are warranted, immunohistochemical analysis suggests that the variant may play a role in the development of the adrenocortical component in CMMT. These results also provide a novel mechanistic insight into the pathogenesis of CMMT.

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Additional Information

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Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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