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Case Report

A Rare Case: Adrenal Corticomedullary Mixed Tumor With Elements of Pheochromocytoma, Cortical Adenoma, and Ganglioneuroma Cells

Erica Patel, MD [1,*], Yufei Chen, MD [2], Xuemo Fan, MD, PhD [3], Ning-Ai Liu, MD, PhD [1], Anne Marie Westreich, MS, CGC [4], Kathryn Reyes, MS, CGC [4], Artak Labadzhyan, MD [1]

[1] Division of Endocrinology and Metabolism, Cedars-Sinai Medical Center, Los Angeles, California
[2] Division of Surgery, Cedars-Sinai Medical Center, Cedars-Sinai Medical Center, Los Angeles, California
[3] Division of Pathology, Cedars-Sinai Medical Center, Los Angeles, California
[4] Division of Medical Genetic, Cedars-Sinai Medical Center, Los Angeles, California

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ABSTRACT

Background/Objective: Adrenal corticomedullary mixed tumor (CMMT) are extremely rare single adrenal tumor masses containing a mixture of adrenal cortical adenoma and pheochromocytoma cells.
Case Report: A 52-year-old woman presented with clinical and biochemical evidence of cortisol and catecholamine excess and was found to have an adrenal CMMT with intermixed chromaffin, cortical adenoma, and ganglioneuroma components. She underwent a successful unilateral adrenalectomy with subsequent improvement in her symptoms.
Discussion: We report the first case of a patient with a CMMT that had symptoms of both catecholamine and cortisol excess from her tumor. Typically, patients with similar tumors have signs of cortisol excess; however, the pheochromocytoma portion is clinically silent. Although most CMMT contain 2 distinct cell types, this is the third ever described case of a single adrenal CMMT containing 3 unique cellular components: (1) intermixed chromaffin, (2) cortical adenoma, and (3) ganglioneuroma cells.
Conclusion: Our understanding of these rare tumors is limited, and this case serves to broaden our knowledge about their clinical, biochemical, and pathologic features.

Introduction

An adrenal corticomedullary mixed tumor (CMMT) is an adrenal mass containing both adrenal cortical adenoma and pheochromocytoma cells. This tumor is extremely rare, with only 20 cases reported to date. We present the clinical, biochemical, and pathologic features of an adrenal CMMT composed of pheochromocytoma, cortical adenoma, and ganglioneuroma components. This patient is the third ever described case of a single adrenal CMMT containing 3 distinct cellular components and the first case described with symptoms of both excessive catecholamine and cortisol from this type of tumor. This case serves to add to the breadth of our understanding about the composition of CMMTs and their associated clinical findings.

Case Report

A 52-year-old woman with type 2 diabetes mellitus and hypertension diagnosed 4 months prior presented for evaluation of an adrenal mass that was incidentally found on computed tomography performed for spondylolisthesis. Imaging showed a heterogeneous enhancing right adrenal mass measuring 3.4 × 3.0 cm and 37, 104, and 57 HU at the precontrast, venous, and delayed phases, respectively (Fig. 1). Three years prior to presentation, she sustained a left wrist fracture following a ground level fall. One year prior to presentation, she developed palpitations, worsening anxiety, and increase in central obesity with a 12-kg weight gain despite moderate-intensity exercise. Four months prior to presentation, she experienced easy bruising with minor trauma and proximal muscle weakness.

Abbreviations: ACTH, adrenocorticotropic hormone; CMMT, corticomedullary mixed tumor.

* Address correspondence to Dr Erica Patel, Division of Endocrinology and Metabolism, Cedars-Sinai Medical Center 8700 Beverly Blvd Becker #131 Los Angeles, CA 90048.
E-mail address: erica.patel@cshs.org (E. Patel).

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She denied the use of glucocorticoids, herbal supplements, or other over-the-counter supplements. Active medication included metformin 1000 mg twice a day.

The patient's weight and height were 58 kg and 1.5 m, respectively, with a body mass index of 25.8 kg/m^2. Her blood pressure was 150/92 mm Hg with heart rate of 90 beats/minute. Physical examination was notable for anxiety, abdominal obesity, thinning muscle bulk in her extremities, and decreased proximal strength bilaterally. No hirsutism, purple striae, or thinning of skin was noted.

The blood cell count and electrolyte levels were within the normal limits. Both the urine and plasma metanephrine levels were markedly elevated. The plasma metanephrine, plasma normetanephrine, 24-hour urine metanephrine, and 24-hour urine normetanephrine levels were 4.69, 3.31, 7.25, and 1.3 times the upper limit of normal. The patient had a nonsuppressed morning cortisol level of 22.6 μg/dL with a dexamethasone level of 300 ng/dL after a 1-mg low-dose dexamethasone suppression test, and the 24-hour urine cortisol was elevated at 53.6 μg. The plasma adrenocorticotropic hormone (ACTH), obtained at the time of 24-hour urine cortisol assessment without dexamethasone suppression, was undetectable. The plasma renin and aldosterone levels were normal. The complete preoperative laboratory data are shown in Table 1.

The patient was diagnosed with pheochromocytoma with concomitant Cushing syndrome. Phenoxybenzamine was initiated preoperatively, and the dose was titrated up to 50 mg twice a day. Metoprolol was added later for treatment of tachycardia. She underwent a laparoscopic right adrenalectomy without complication. Stress-dose hydrocortisone was started perioperatively and continued after surgery. Postoperative course was unremarkable, and the patient was discharged home on hospital day 2.

Gross sectioning revealed a 4.1 × 3.5 × 2.7-cm mass. The cut surface displayed 2 distinct areas: (1) tan-pink area and (2) golden-yellow and red-brown area with focal hemorrhage. The mass appeared to arise within the medulla, with a thin rim of the golden-yellow cortex around the periphery. The mass focally extended through the cortex into the surrounding adipose tissue (Fig. 2 *A*, arrow). The remainder of the adrenal gland was grossly unremarkable.

Microscopically, the tumor was characterized by a mixture of pheochromocytoma and adrenocortical adenoma components creating a composite tumor having both cortical and medullary characteristics (Fig. 2 *A* through *F*). In addition, there was an admixed component of ganglioneuroma. Focally, there was an extracapsular extension by the pheochromocytoma component into surrounding adipose tissue. However, there was no evidence of other aggressive features, such as marked nuclear atypia, nuclear hyperchromasia, brisk mitosis, atypical mitosis, diffuse growth, tumor necrosis, vascular invasion, or high cellularity. Immunohistochemical stains of the pheochromocytoma component were positive for chromogranin and synaptophysin, and a few cells exhibited ACTH immunoreactivity. The adrenocortical adenoma component was positive for inhibin. Tumor cells showed no loss of succinate dehydrogenase B immunoreactivity.

The comprehensive genetic evaluation results of 91 genes, including FGFR4 as well as other mutations associated with pheochromocytoma in familial syndromes, were negative. Two variants of undetermined significance were identified in the genes CDKN1B (c.397C>A) [p.P133T variant] and TSC1 ([c.3127_3129dupAGC] [p.S1043dup variant]).

The patient had marked clinical improvement following unilateral adrenalectomy. Her hypertension and palpitations resolved,

Highlights

- Adrenal corticomedullary mixed tumors are unique tumors are usually characterized as a single mass that contains both adrenal cortical and chromaffin cells intermixed in the same neoplasm. Rarely, they can contain more than 2 components as in the case of this patient
- They are likely to occur in females, and most are benign with a favorable prognosis
- Although most exhibit signs of excessive cortisol, they rarely can cause symptoms of both pheochromocytomas and Cushing syndrome.

Clinical Relevance

This patient is the third ever described case of a single adrenal corticomedullary mixed tumor containing 3 distinct cellular components: (1) ganglioneuroma, (2) adrenal cortical, and (3) pheochromocytoma cells. She is the first reported case of a patient with symptoms of both excessive catecholamine and cortisol from this tumor. This serves to broaden our knowledge about their clinical, biochemical, pathologic, and imaging features.

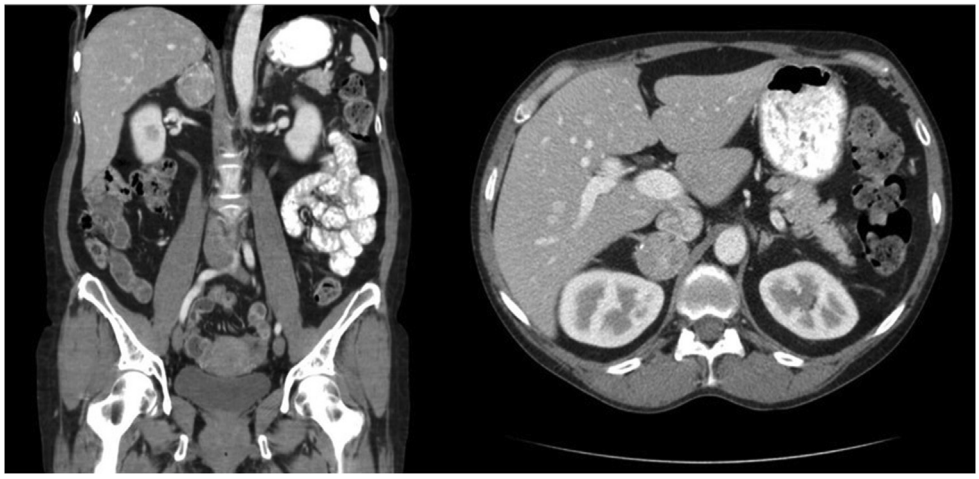

Fig. 1. Preoperative abdominal computed tomography scan showing a 3.4 × 3.0-cm heterogeneously enhancing right adrenal mass.

Table 1
Preoperative Endocrinology Evaluation

Test	Value	Reference range
Plasma metanephrines	2.39	0-0.49 nmol/L
Plasma normetanephrines	2.95	0-0.89 nmol/L
24-h urine metanephrine, μg/24 h	1660	36-229
24-h urine normetanephrine, μg/24 h	829	95-650
24-h urine free cortisol, μg/24 h	53.6	4-50
24-h urine creatinine, g/24 h	0.91	0.50-2.14
24-h urine volume/24 h	1400	N/A
Morning cortisol following 1-mg dexamethasone taken at 11 PM the night prior, μg/dL	28.57	4-22
Dexamethasone level following 1-mg dexamethasone taken at 11 PM the night prior, μg/dL	300	>200 ng/dL
Salivary cortisol #1, μg/dL (11 PM)	0.20	<0.09 (11 PM)
Salivary cortisol #2, μg/dL (11 PM)	0.22	<0.09 (11 PM)
Salivary cortisol #3, μg/dL (11 PM)	0.20	<0.09 (11 PM)
ACTH, pg/mL	<5	6-50
DHEA-S, μg/dL	88	23-266
Total testosterone, ng/dL	15	2-45
Free testosterone, pg/mL	1.8	0.1-6.4
Plasma renin activity (ng/mL/h)	1.6	0.5-4
Aldosterone, ng/dL	25	4-31
TSH, mIU/mL	1.03	0.4-4.0

Abbreviations: ACTH = adrenocorticotropic hormone; DHEA-S = dehydroepiandrosterone sulfate; TSH = thyroid-stimulating hormone.

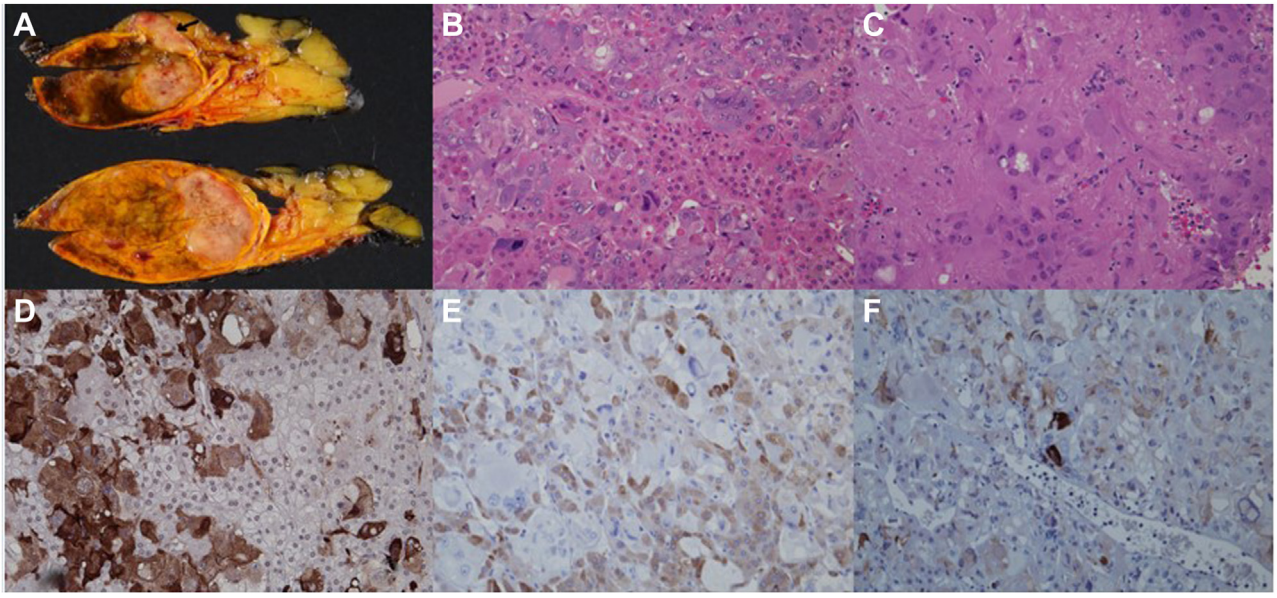

Fig. 2. Pathology. *A*, The gross cut surface of the tumor. *B*, Hematoxylin and eosin stain demonstrating intermixed chromaffin (large basophilic cells with large nuclei) and adrenocortical adenoma cells (eosinophilic cytoplasm with small rounded nuclei). *C*, Ganglioneuroma component. *D*, Chromogranin stain highlighting pheochromocytoma cells. *E*, Inhibin stain highlighting adrenocortical adenoma cells. *F*, Focal adrenocorticotropic hormone staining in pheochromocytoma cells. All micrographs at ×200 magnification.

Table 2
1-Month Postoperative Hormonal Evaluation

Test	Value	Reference range
24-h urine metanephrine, μg/24 h	9	36-229
24-h urine normetanephrine, μg/24 h	41	95-650
Plasma normetanephrine, nmol/L	0.31	<0.90
Plasma metanephrine, nmol/L	<0.20	<0.50

and her muscle weakness improved. The plasma metanephrine level was normal, and the 24-hour urine metanephrine and normetanephrine levels were low according to the laboratory results obtained 1 month postoperatively (Table 2). She was continued on a prolonged steroid taper with a planned cosyntropin test in the future to assess for recovery of adrenal function.

Discussion

Adrenal CMMTs are more likely to occur in females, and most are benign with a favorable prognosis.[1] These unique tumors are usually characterized as a single mass that contains both adrenal cortical and chromaffin cells intermixed in the same neoplasm.[2] This is different from rare but more common tumors such as adrenal cortical adenomas and pheochromocytomas that occur in the same adrenal gland, pheochromocytoma with entrapped nonneoplastic cortical cells, and pheochromocytoma with cortical hyperplasia.[3] This distinction can generally be made based on histologic findings that show an intermixed population of chromaffin and cortical cells. Immunohistological staining can confirm the variegated nature of the tumors. The adrenal cortical component is characteristically positive for alpha inhibin, whereas the medullary component is positive for chromogranin and synaptophysin.[4]

Our patient had a highly unusual tumor, consisting of components of pheochromocytoma, cortical adenoma, and ganglioneuroma. This combination of 3 types of mixed cell types in an adrenal tumor has only been previously described twice in the literature by Lau et al.[4] and Aiba et al.[5] Clinical symptoms may occur due to any component of the tumor. A majority of corticomedullary tumors that contain both pheochromocytoma and cortical adenoma components have been associated with Cushing syndrome due to hypercortisolemia, whereas the pheochromocytoma portion remains clinically silent.[1,3,6,7] In the case described by Lau et al,[4] the patient had symptoms consistent with Cushing syndrome; however, the concurrent pheochromocytoma was not discovered until the pathology was evaluated. Our patient had significant symptoms related to catecholamine and cortisol excess, which demonstrates the uniquely robust secretion of both the chromaffin and cortical adenoma cells in her tumor.

The pathogenesis of these tumors has been subject to debate with multiple theories about their origin. Ganglioneuromas are rare, differentiated cells arising from neural crest tissue that are hormonally silent. Thirty percent of patients with ganglioneuromas have elevated plasma and urinary catecholamine levels without exhibiting any symptoms of excess.[1] Composite pheochromocytomas, composed of pheochromocytomas and ganglioneuromas, have been attributed to the shared embryologic origin of chromaffin and neuronal cells from the neural crest with the potential for chromaffin cells to undergo aberrant cellular differentiation into neuronal elements.[8]

In contrast, cortical and chromaffin cells are of different embryologic derivation without the potential for abnormal differentiation; their etiology is more elusive. One hypothesis is that ACTH or growth factors derived from the pheochromocytoma components may cause an ectopic adrenocortical neoplasm.[9] In our case, although the tumor stained weakly positive for ACTH in a few pheochromocytoma cells, the patient had ACTH-independent Cushing syndrome because the ACTH was suppressed, and she did not have bilateral adrenal hyperplasia on imaging. Interestingly, the dehydroepiandrosterone sulfate, renin activity, and aldosterone levels were normal, which are typically low or suppressed in ACTH-independent Cushing syndrome.[10,11] We speculate that there may have been cyclical ACTH production by the tumor with paracrine action leading to normal dehydroepiandrosterone sulfate level and that the degree of hypercortisolism was likely not enough to alter the aldosterone and renin levels.

The genetic origin of mixed tumors remains undefined. Kanzawa et al[12] identified a corticomedullary mixed adrenal tumor containing an *FGFR4*-G388R variant. They hypothesized that this variant may play a role in the development of the adrenocortical component within the pheochromocytoma, leading to CMMT Germline homozygous *FGFR4*-G388R has also previously been reported to be associated with poor prognosis and disease progression in several neoplasms, including breast, colon, prostate, skin, lung, head and neck, sarcoma, and endocrine tumors.[12] The FGFR4 variant was negative in our patient and not likely contributing to the pathogenesis. Our patient had the CDKN1B variant, which has been associated with multiple endocrine neoplasia type 4 that includes adrenal tumors. However, this test is not designed to differentiate germline mutations from somatic mutations and was determined to not be of clinical significance.

Conclusion

Given the extremely rare nature of this tumor, we have limited insight into the long-term clinical course. Fortunately, of the cases reported to date, they have had benign clinical courses with no instances of metastasis or death due to the disease, including 1 case that had histologic malignant transformation to a spindle cell sarcoma.[3] The presence of ganglioneuroma, a benign entity in the absence of neuroblastic components, also portends a favorable outcome. Prognosis is primary related to the metabolic features resulting from catecholamine and cortisol excess. Recurrence of the tumor on the contralateral adrenal gland has been described in 1 case of the literature.[4] Thus, long-term follow up is recommended.

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