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CASE REPORT

# Co-Existing Ectopic Cortisol-Producing Adenoma and Retroperitoneal Schwannoma, a Rare Case Report

Lingfeng Shi[1], Jiongyu Hu[1], Xiaoli Xu[2], Yongquan Wang[3], Senlin Xu[4], Lijuan Tu[2]

[1]Endocrinology Department, First Affiliated Hospital of Third Military Medical University (Army Medical University), Chongqing, People's Republic of China; [2]Third Military Medical University (Army Medical University), Chongqing, People's Republic of China; [3]Urology Department, First Affiliated Hospital of Third Military Medical University (Army Medical University), Chongqing, People's Republic of China; [4]Pathology Department, First Affiliated Hospital of Third Military Medical University (Army Medical University), Chongqing, People's Republic of China

Correspondence: Lijuan Tu, Email 251881081@qq.com



**Background:** Ectopic cortisol-producing adrenocortical adenoma (ECPA) is extremely rare, with only a few cases reported. Retroperitoneal schwannoma is also uncommon, accounting for only 0.7–5% of all schwannomas. It is peculiar to have both conditions at the same time, and it is intriguing to explore their possible connection. Herein, we present a case of both ECPA and retroperitoneal schwannoma and provide our conjectures regarding their co-occurrence.

**Case Presentation:** A 38-year-old female presented with a two-year history of facial and lower limb edema, as well as chest tightness and palpitations for the past four months. Physical examination revealed hypertension, a high body mass index (BMI), moon face, thick neck and back fat, abdominal obesity, and purple striae on the abdomen. Laboratory tests indicated an persistent increased cortisol level and suppression of adrenocorticotropic hormone (ACTH). Adrenal-enhanced computed tomography (CT) scan showed that both adrenal glands appeared normal without evident adenomas or hyperplasia. However, the scan revealed two lesions located in the right renal hilum and retroperitoneal area positioned anteriorly to the lower margin of the lumbar 2 pyramid. Further imaging using $^{68}$Ga-DOTATATE PET/CT revealed concentrated radiotracer uptake in the tumor at the right renal hilum, indicating it may be responsible for the patient's Cushing's symptoms. After laparoscopic resection of these masses, clinical symptoms improved significantly. Postoperative pathology confirmed the right renal hilum one lesion as an ECPA while identifying another lesion as a schwannoma.

**Conclusion:** Our literature reported a case with the diagnosis of both ECPA in the right renal hilum and retroperitoneal schwannoma. $^{68}$Ga-DOTATATE PET/CT imaging can provide functional and locational information on tumors, enabling a comprehensive examination of the entire body to identify lesions that require appropriate treatment.

**Keywords:** ectopic adrenocortical adenoma, schwannoma, cortisol-producing adrenocortical adenomas, Cushing syndrome, case report

## Introduction

Cushing's syndrome (CS) can be categorized into adrenocorticotropic hormone (ACTH)-dependent or independent subtypes. Ectopic adrenocortical adenoma is an infrequent subtype of ACTH-independent CS, which originates from the intermediate mesoderm during embryonic development and is primarily caused by the abnormal persistence of adrenocortical tissue along the embryonic migration path within the urogenital tract.[1] The majority of ectopic adrenocortical tissues are non-functional, making ectopic cortisol-producing adrenocortical adenoma (ECPA) an exceedingly uncommon occurrence.[2]

Schwannomas are nerve sheath tumors derived from Schwann cells that appear sporadically. In the peripheral nervous system, schwannomas typically manifest following or in close proximity to the spine and exhibit a spatial association with vertebral bones or the vertebral canal.[3] The exact aetiology of schwannomas remains unclear. However, current

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evidence have found that both genetic variations such as *nf2* and the tumorigenic environment could significantly contribute to their occurrence and development.[4]

We hereby present an intriguing case involving the simultaneous detection of ECPA and schwannoma. Additionally, we postulate a potential association between these two distinct tumors. To our knowledge, no such case has been reported.

## Case Presentation

The patient was a 38-year-old woman who had been presented with facial and lower limb edema persisting for nearly two years, accompanied by abdominal purple striae, hypertension, high body mass index (BMI), moon face and abdominal obesity. Four month prior to diagnosis, She experienced chest tightness and palpitations during physical activity, prompting her to seek medical evaluation at a local hospital. Given the disturbance of the circadian rhythm of cortisol and elevated midnight plasma cortisol level along with corresponding symptoms observed in the patient, her physician suspected CS. However, the bilateral adrenal ultrasound and subsequent magnetic resonance imaging (MRI) of the pituitary gland did not reveal any tumors. Consequently, the patient was referred to our department for further confirmation.

We initially confirmed the diagnosis of ACTH-independent CS by assessing ATCH levels and conducting an overnight low-dose dexamethasone suppression test. At 8 am on the first day, her plasma cortisol concentration was 1444.80 nmol/L (normal range: 181.83–787.93 nmol/L), while her ACTH concentration was less than 1.00 pg/mL (normal range: 5–60 pg/mL). On the second day at 8 am, her cortisol concentration measured 942.31 nmol/L.

Next, we performed adrenal computed tomography (CT) due to its superior visualization capabilities compared to ultrasound. Consistent with previous findings, the results showed normal bilateral adrenal morphology without any evident abnormal enhancement. However, the CT image also revealed two masses: one located in the right renal hilum and the other in the retroperitoneal area positioned anteriorly to the lower margin of the lumbar 2 pyramid, measuring approximately 30*28mm and 16*16mm, respectively (Figure 1A and B).

After excluding ectopic pheochromocytoma based on normal plasma levels of catecholamine-related hormones, we established a diagnosis of ectopic adrenocortical adenoma for the patient. To assess the presence of additional tumors and determine their endocrine functionality, positron emission tomography (PET) computed tomography (CT) with 68Ga-DOTATATE (68Ga-DOTA) was conducted for neuroendocrine tumor visualization. Fortunately, only two masses were detected in her body which is consistent with the adrenal CT findings. The mass located in the right renal hilum exhibited a concentration of imaging agent (Figure 1C and D).

After low dose hydrocortisone replacement during the perioperative period, the surgical excision of both tumors was performed following their precise localization (Figure 2A and B). The larger brown tumor measuring 30*28*25mm was situated in the right renal hilum region, and subsequent histopathological analysis confirmed its diagnosis as an ectopic adrenocortical adenoma. Through histopathological examination, the smaller yellow tumor measuring 15*13*10mm, located in the retroperitoneal area, was identified as a schwannoma (Figure 2C–F).

On the second postoperative day, despite the ACTH level remaining below 1.00 pg/mL, her plasma cortisol level at 8 am decreased to 283.11 nmol/L. To prevent hypocortical crisis, we continue to conduct a two-week physiological corticosteroid supplementation therapy after the operation and gradually tapered it over an 8-week period based on clinical symptoms and morning plasma cortisol and ACTH levels (Table 1). No signs of CS recurrence were observed during the total 4-month postoperative follow-up.

## Discussion

We here report a case of coexisting ECPA and schwannoma. During embryogenesis, the mesoblast begins to proliferate and differentiate during the fifth week of gestation, and eventually forms adrenocortical cells.[5] Ectopic adrenal glands occur when there are remnants of adrenal tissue along the path from the gonads to the adrenal glands during embryonic development. Such ectopic glands has been found in various locations including celiac plexus, kidney, broad ligament, epididymis, and testis.[6,7] In our case, an ectopic adrenal adenoma was found in the renal hilum. A literature review revealed seven previously reported cases of ectopic adrenal adenomas at this location.[8–14] However, these ectopic adrenal

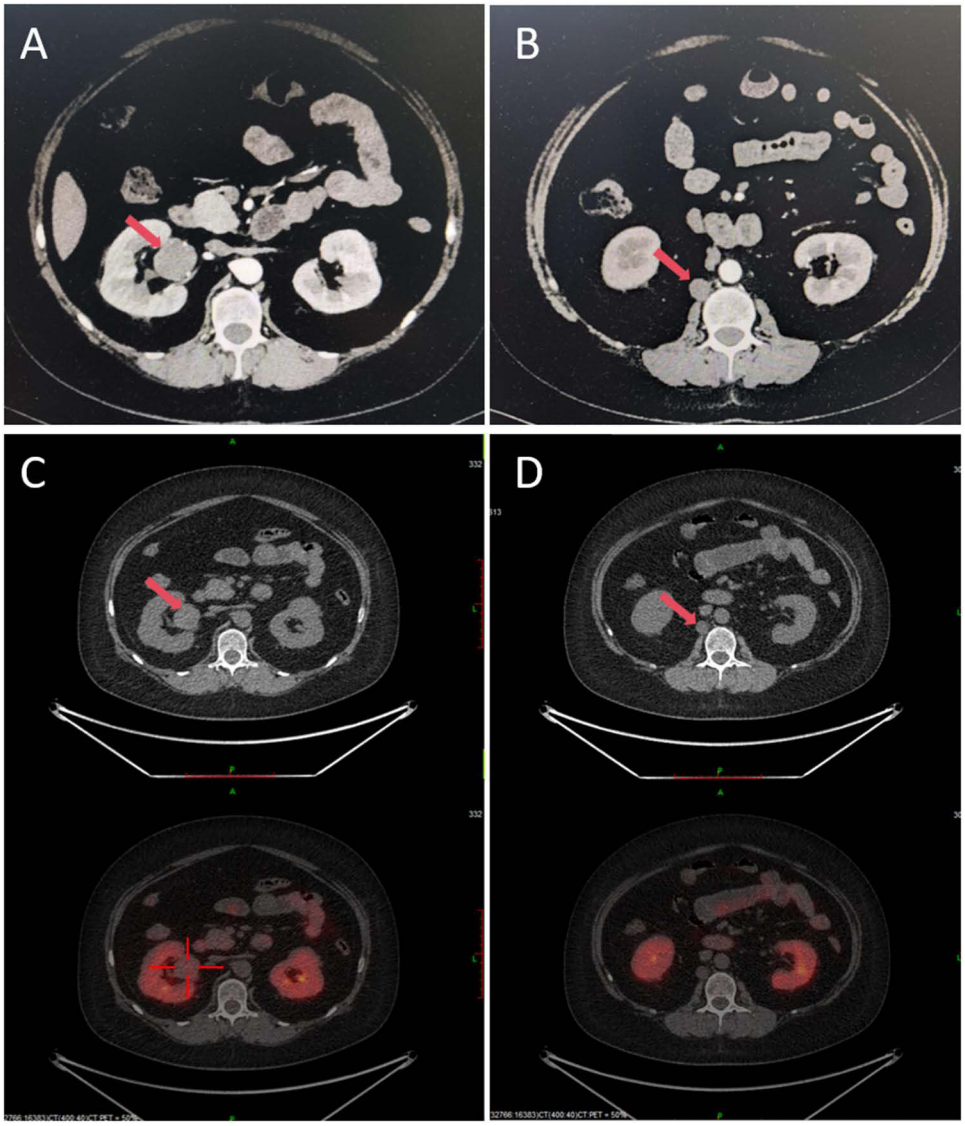


**Figure 1** Radiological images of the patient. (**A** and **B**) The computed tomography (CT) images depict tumors in the right renal hilum (**A**) and retroperitoneal area (**B**). (**C** and **D**) Positron emission tomography (PET)-CT with 68 Ga-DOTATATE images of the right renal hilum (**C**) and retroperitoneal area (**D**). The red arrows indicate the tumors, and the red cross indicates the agent concentration in the tumor.

adenomas can manifest differently, either as non-functional tumors or hormonal disorders like Cushing's syndrome, hyperaldosteronism, and testosterone elevation. Among the seven cases, only two involved ECPA located in the renal hilum area.[11,12] On the other hand, schwannoma originates from ectodermal tissues and is a rare neoplasm arising from Schwann cells within nerve myelin sheaths.[15] Based on its origin, schwannoma do not secrete hormones, and most patients remain asymptomatic. Primary schwannomas can be found across various anatomical sites. One "failure-of-nerve regeneration" theory indicated that the tumor may develop following nerve crush injury, thereby favoring anatomical locations prone to physical stress and injury.[16] Our patient presented with a retroperitoneal schwannomas anteriorly positioned below lumbar 2 pyramid margin, which is in accordance with this theory.

Another challenge for the patient lies in discerning the hormone-secreting nature of these tumors. Although our initial adrenal CT scan provided morphological information, it failed to ascertain their endocrine function. Upon reviewing relevant literature, we came across a recent report that utilized $^{68}$Ga-DOTA PET/CT imaging to unveil ACTH-independent Cushing syndrome caused by ectopic adrenocortical adenoma.[17] Importantly, $^{68}$Ga-DOTA PET/CT has been increasingly employed for detecting neuroendocrine tumors and yielded successful outcomes in our previous

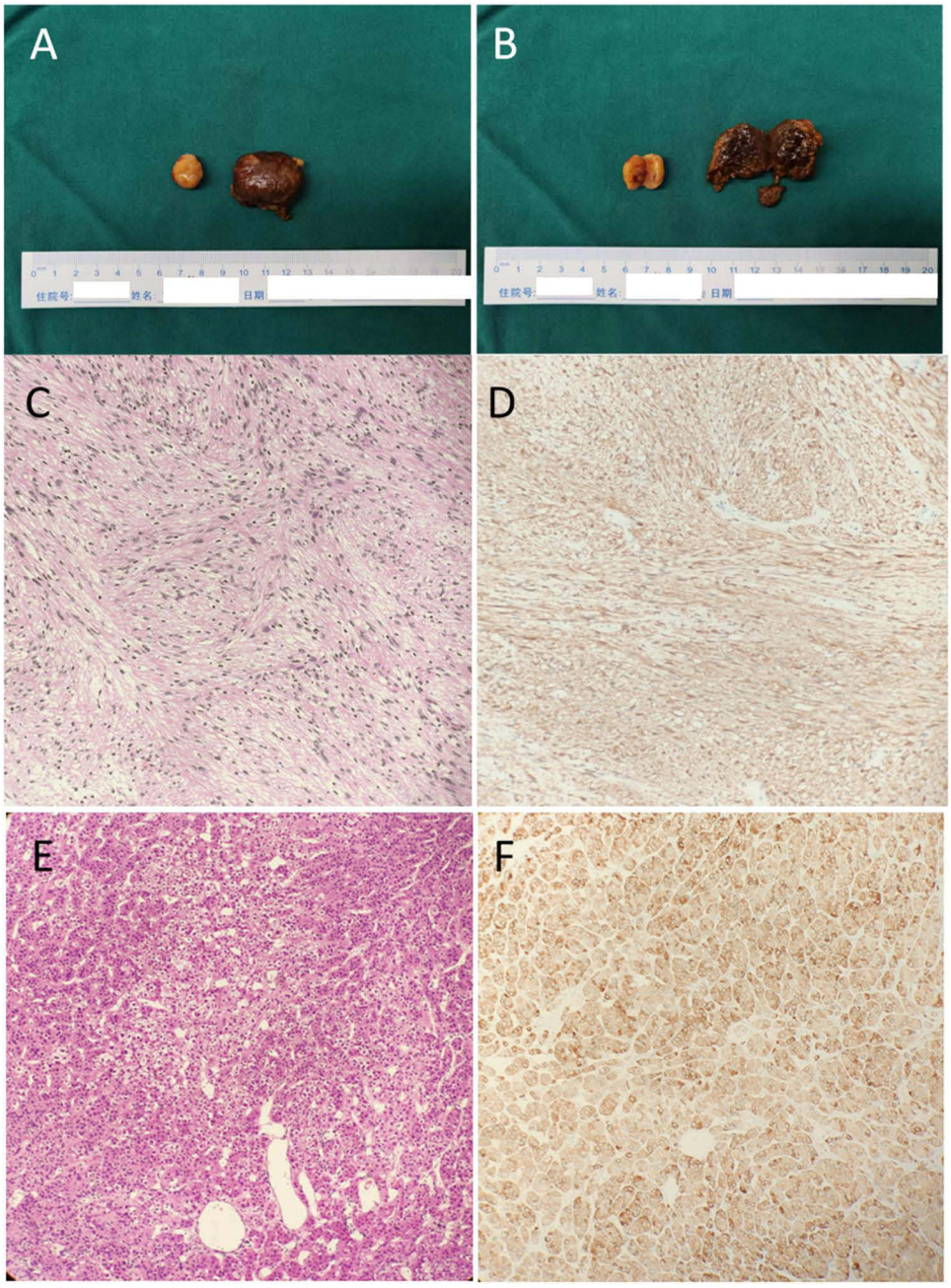


**Figure 2** Tumors morphology and pathological images. (**A** and **B**) The appearance and incision of both tumors. The smaller yellow one (left) from patient's retroperitoneal area, and the larger brown one (right) from patient's right renal hilum. (**C** and **D**) The retroperitoneal tumor (schwannoma) is shown through H&E staining (**C**) and AC100 immunohistochemical staining (**D**). (**E** and **F**) The renal hilum tumor (ectopic adrenocortical adenoma) is displayed through H&E staining (**E**) and inhibin immunohistochemical staining (**F**).

neuroendocrine case.[18] Consequently, we ultimately conducted a $^{68}$Ga-DOTA PET/CT scan which effectively differentiated the endocrine function of each tumor. Subsequently, surgical removal of both tumors was performed considering the potential malignancy and the ECPA. As anticipated, postoperative histopathological examination confirmed one tumor as an ECPA and the other as a schwannoma.

There still a question remains worth discussing, namely whether these two tumors are completely unrelated and coincidental or if there exists a potential connection between them. We considered the possibility of Carney complex (CNC), as its clinical manifestations can also involve CS and schwannomas. However, the speculation was not confirmed due to the absence of primary pigmented nodular adrenocortical disease, myxoma, or a family history of CNC.

**Table 1** Serum $K^+$, COR and ACTH Levels During the Hospitalization and 4 Month Follow-Up

| Parameter | At Diagnosis | The Second Day After Operation | One month After Operation | Two month After Operation | Four month After Operation | Reference Range |
|---|---|---|---|---|---|---|
| $K^+$(mmol/L) | 3.20 | 3.62 | 3.82 | 3.24 | 4.17 | 3.5–5.5 |
| COR(nmol/L) | 1444.80 | 283.11 | 194.53 | 346.18 | 384.71 | 181.83–787.93 |
| ACTH(pg/mL) | <1.00 | <1.00 | <1.00 | <1.00 | 11.62 | 5–60 |

**Abbreviations**: $K^+$, serum potassium; COR, serum cortisol; ACTH, serum adrenocorticotropic hormone.

Furthermore, there is currently no documented association between silent mutation of neurofibromatosis type 2 (*nf2*), an important genetic cause of schwannomas, and cortisol-secreting tumors. Therefore, we have not identified direct connections between the two tumors. Nevertheless, we still hold some conjectures regarding their potential associations. Firstly, according to current understanding, ectopic adrenal tissue anatomically originates from dispersed fragments of adrenal tissue along its migratory route during embryogenesis. The patient's retroperitoneal schwannoma, a rare occurrence representing only 0.7–5% of all schwannomas,[19] happened to be located in this migratory path. It is reasonable to suppose whether the scattered fragments also resided in the retroperitoneal area at that moment and degenerated during aging, or somehow injured the area during their migration. These factors may have rendered the area more vulnerable to other damage, such as physical stress, and increase the likelihood of developing schwannoma according to the "failure-of-nerve regeneration" theory. The second speculation is based on the genetic changes in tumorigenesis. As previously mentioned, silent mutation of *nf2* play a crucial role in the genetic cause of schwannomas. Additionally, CNC, which can involve CS and schwannomas, primarily arises from inactivating mutations of the type 1A regulatory subunit of protein kinase A (*PRKAR1A*), thereby affecting other proteins involved in the pathogenesis of schwannoma such as inhibiting NF2 signaling.[20] Furthermore, genetic alterations have have been identified in cortisol-producing adrenocortical tumors including GNAS, PRKAR1A, PRKACA, PRKACB, PDE11A, and PDE8B.[21] It is reasonable to hypothesize whether a genetic cause could explain the co-occurrence of these tumors in the patient.Lastly, the tumor microenvironment may additionally contribute to the intricacy of co-occurring tumors. For instance, most benign cortisol-producing adrenocortical tumors are regulated by aberrant cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA) signaling,[21] which also plays a pivotal role in schwannoma development.[22] Various tumor growth factors such as insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) have been demonstrated to activate downstream cAMP-PKA pathways in both types of tumors. However, the concept of tumor microenvironment is multifaceted and necessitates further investigation.

## Ethics Approval

Written informed consent was obtained from the patient and The Ethics Committee of First Affiliated Hospital of Third Military Medical University (Army Medical University) for publication of any potentially identifiable images or data included in this article.

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## Disclosure

The authors declare that they have no competing interests.

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