JCEM Case Reports, 2025, **3**, luaf027
https://doi.org/10.1210/jcemcr/luaf027
Advance access publication 10 February 2025
Case Report

Adrenocorticotropin-Secreting Pure Adrenal Ganglioneuroma Leading to Cushing Syndrome

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Abstract

Adrenal ganglioneuromas (AGNs) are rare benign neoplasms of neural crest origin that are typically asymptomatic and endocrinologically inactive. However, on occasion, AGNs have been noted to demonstrate secretion of various hormones. We present a case of a 23-year-old man who presented with hypertension and clinical symptoms concerning for a catecholamine excess state with evidence of a right adrenal mass with elevated Hounsfield units (HU) on abdominal computed tomography (CT) and laboratory values consistent with mild hypercortisolism concerning for adrenocorticotropin (ACTH)-producing pheochromocytoma leading to Cushing syndrome (CS). The patient underwent adrenalectomy with pathology results demonstrating a pure AGN with positive ACTH staining. While secretory AGNs are rare, it is important that providers remain cognizant of this pathology and consider it within the evaluation of adrenal lesions at large with an understanding that clinical presentation may be difficult to interpret and will likely vary based on the underlying hormone(s) being secreted. Additionally, secretory AGNs can mimic other adrenal neoplasms and histopathologic evaluation is required for definitive diagnosis. This case demonstrates how ACTH-producing AGNs should be considered when evaluating cases of ACTH-dependent CS.

Key Words: adrenal tumor, ganglioneuroma, adrenal ganglioneuroma, Cushing syndrome

Abbreviations: 17-OH progesterone, 17-hydroxyprogesterone; ACTH, adrenocorticotropin; AGN, adrenal ganglioneuroma; CP, composite pheochromocytoma; CRH, corticotropin-releasing hormone; CS, Cushing syndrome; CT, computed tomography; DHEA-S, dehydroepiandrosterone sulfate; LDDST, low-dose dexamethasone suppression test.

Introduction

There are numerous etiologies that precipitate Cushing syndrome (CS) but one less common cause is an adrenocorticotropin (ACTH)-secreting pure adrenal ganglioneuroma (AGN), which is a rare neoplasm. AGNs are typically benign, well differentiated, and slow-growing neural crest–derived neoplasms that are usually asymptomatic and hormonally inactive. As a result, most AGNs are identified as incidentalomas [1, 2]. However, an AGN may rarely be secretory, mimicking other adrenal pathologies (particularly a pheochromocytoma) thereby making it difficult to establish a preoperative diagnosis. Here, we report the second documented case of ACTH-dependent CS secondary to an ACTH-producing pure AGN.

Case Presentation

A 23-year-old male patient with a past medical history significant for migraine without aura presented for evaluation of hypertension (noted by his pediatrician during a routine wellness visit). The patient was initially referred to cardiology for evaluation and management of his hypertension where computed tomography (CT) imaging was performed, revealing a right adrenal mass measuring 3.1 cm × 2.6 cm and with an unenhanced CT attenuation of 24 Hounsfield units (HU) and 42 HU post contrast. Subsequently, he was referred to endocrinology where work-up revealed normal late-night salivary cortisol but elevated 24-hour urine free cortisol and lack of full cortisol suppression on low-dose dexamethasone suppression test (LDDST). Also, the patient endorsed associated anxiety, mental stress (from various external sources such as school and work), as well as excessive sweating but denied weight changes, easy bruising, poor sleep, or history of hyperglycemia, which was confirmed on laboratory review. The patient underwent puberty at a normal age. Additionally, he denied substance use or relevant family history.

Diagnostic Assessment

Physical examination was significant for elevated blood pressure of 168/107 mm Hg and tachycardia to 134 beats per minute. Additionally, he demonstrated a small degree of facial

Received: 11 December 2024. **Editorial Decision:** 29 January 2025. **Corrected and Typeset:** 10 February 2025

Table 1. Preoperative and postoperative laboratory testing performed as part of initial hypercortisolism work-up and routine postprocedural biochemical follow-up

Comparison of preoperative and postoperative hormonal laboratory panels			
Laboratory test	**Values**		**Normal reference ranges**
	Preoperative value	**Postoperative value**	
24-h Urine free cortisol	133 μg/24 h; 367 nmol/24 h	41 μg/24 h; 113.2 nmol/24 h	5-64 μg/24 h; 13.8-176.6 nmol/24 h
AM Cortisol, during LDDST	4.7 μg/dL; 129.7 nmol/L	Not completed postoperatively	<1.8 μg/dL; <50 nmol/L
AM ACTH, during LDDST	6.2 pg/mL; 1.4 pmol/L	Not completed postoperatively	<2.7 pg/mL; 0.6 pmol/L
ACTH	29.1 pg/mL; 6.4 pmol/L	24.9 pg/mL; 5.5 pmol/L	7.2-63.3 pg/mL; 1.6-13.9 pmol/L
Random serum cortisol, drawn ~0800	20.6 μg/dL; 568.3 nmol/L	19.2 μg/dL; 529.7 nmol/L	AM cortisol 6.2-19.4 μg/dL; 171.1-535.4 nmol/L
DHEA-S	260 μg/dL; 7.0 mmol/L	194 μg/dL; 5.2 mmol/L	164.3-530.5 μg/dL; 4.4-14.3 mmol/L
Testosterone	625 ng/dL; 21.7 nmol/L	631 ng/dL; 21.9 nmol/L	264-916 ng/dL; 9.2-31.8 nmol/L
17-OH progesterone	104 ng/dL; 3.2 nmol/L	111 ng/dL; 3.4 nmol/L	27-199 ng/dL; 0.8-6.0 nmol/L
11-Deoxycortisol	0.09 μg/dL; 0.0026 mmol/L	0.03 μg/dL; 0.0009 mmol/L	<1 μg/dL;<0.0289 mmol/L
Deoxycorticosterone	8.9 ng/dL; 0.27 nmol/L	4.4 ng/dL; 0.13 nmol/L	2-19 ng/dL; 0.06-0.58 nmol/L
Androstenedione	158 ng/dL; 5.5 nmol/L	143 ng/dL; 5.0 nmol/L	27-152 ng/dL; 0.9-40.2 nmol/L
Progesterone	0.40 ng/mL; 1.27 nmol/L	0.30 ng/mL; 0.95 nmol/L	0-0.50 ng/mL; 0-1.59 nmol/L
Plasma metanephrines	<10 pg/mL; <50.7 pmol/L	18.3 pg/mL; 92.8 pmol/L	0-88 pg/mL; 0-446.2 pmol/L
Plasma normetanephrines	45.8 pg/mL; 250.1 pmol/L	57.8 pg/mL; 315.6 pmol/L	0-210.1 pg/mL; 0-1147.1 pmol/L

Preoperative studies were obtained 1 month prior to right adrenalectomy and postoperative studies were obtained 1 to 6 months after right adrenalectomy. LDDST results were analyzed via LabCorp facilities.

Abbreviations: 17-OH progesterone, 17-hydroxyprogesterone; ACTH, adrenocorticotropin; DHEA-S, dehydroepiandrosterone sulfate; LDDST, low-dose dexamethasone suppression test.

plethora but otherwise no stigmata of cushingoid habitus were appreciated and the remainder of the examination was unremarkable. An extensive set of hormonal laboratory tests and repeat 24-hour urine free cortisol were obtained (Table 1). Repeat abdominal imaging was deferred given that the patient already had sufficient imaging demonstrating the right adrenal mass.

Given the presence of an adrenal lesion with high HU, coexistence of presumably catecholamine excess–related symptoms (hypertension, excessive sweating, stress/anxiety), as well as what appeared to be ACTH-dependent hypercortisolism (neither ACTH nor dehydroepiandrosterone sulfate [DHEA-S] were suppressed), there remained a suspicion for an ACTH-secreting pheochromocytoma. However, the findings of baseline normal plasma metanephrines and normal plasma normetanephrines seemed to contradict this hypothesis.

Given the presence of ACTH-dependent hypercortisolism (and despite there being evidence of an adrenal lesion), a magnetic resonance imaging pituitary study was pursued to rule out other potential causes of the patient's hypercortisolism. This was negative for pituitary lesion and overall unremarkable.

Ultimately, the patient was referred to surgery for right adrenalectomy.

Treatment

The patient underwent a right adrenalectomy with the subsequent pathology report detailing findings of a pure AGN (4.7 cm). Given the patient's history of ACTH-dependent CS, immunostaining for ACTH was requested and revealed positive expression (Fig. 1). Of note, the presence of postoperative adrenal insufficiency remains unknown as immediate postoperative cortisol levels were not obtained/assessed, but the patient was empirically maintained on a limited course (1 month total) of supplemental hydrocortisone after the procedure.

Outcome and Follow-up

Postoperative testing (see Table 1) revealed intermittently elevated adrenal precursor hormone levels (ie, androstenedione, deoxycorticosterone, and DHEA-S) and plasma normetanephrines (but normal plasma metanephrines) that eventually

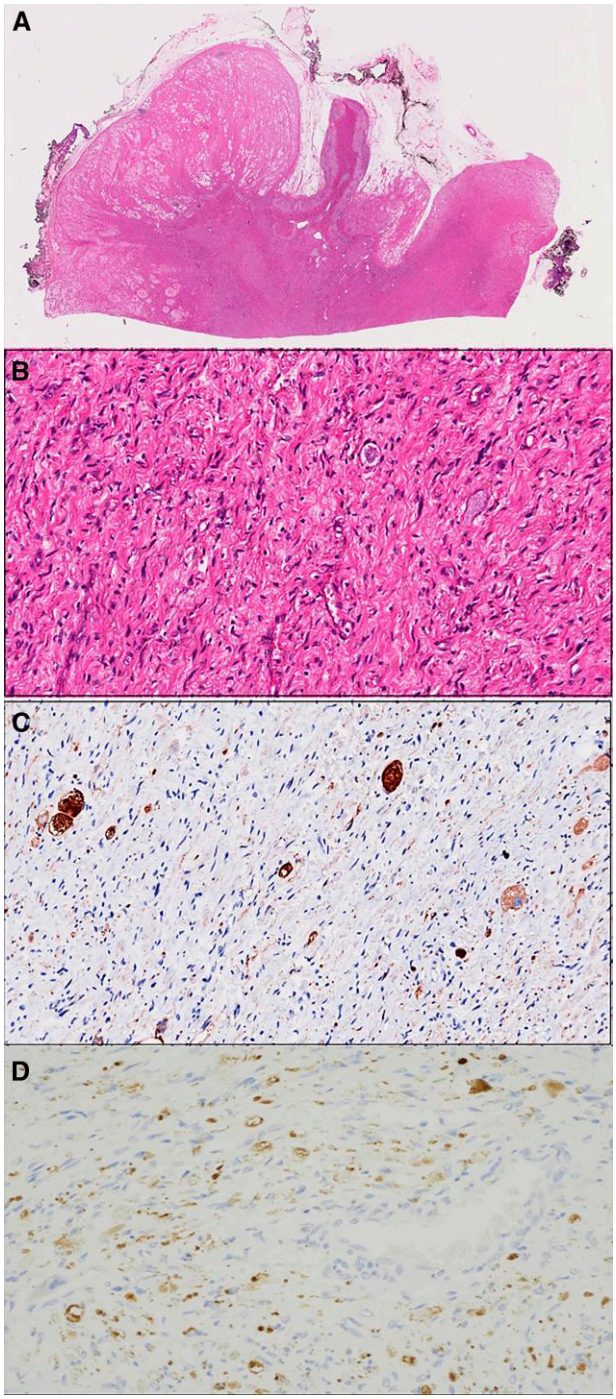

Figure 1. A, Low-power slide with hematoxylin and eosin (H&E) stain demonstrating normal adrenal tissue intermixed within a background of surrounding ganglioneuroma. B, High-power slide with H&E stain of ganglioneuroma tissue. C, High-power slide of ganglioneuroma tissue with staining for synaptophysin. D, High-power slide of ganglioneuroma tissue with staining for adrenocorticotropin.

normalized with time. ACTH and serum cortisol levels were not significantly different pre or post tumor removal, but 24-hour urine free cortisol levels returned to normal after AGN removal.

Clinically, the patient's blood pressure greatly improved in the immediate postoperative setting with largely consistent systolic blood pressure readings ranging from 110 to 120 mm Hg over diastolic blood pressure readings ranging from 60 to 70 mm Hg while off antihypertensive pharmacotherapy. However, the patient did demonstrate one isolated elevated outpatient blood pressure read (1 month postoperatively while on empiric hydrocortisone 10 mg at 0800 and 5 mg at 1300). Given his young age and recent normalization of urine cortisol levels, this elevated reading prompted referral for nephrology evaluation where subsequent renal artery Doppler imaging was negative for renal artery stenosis. Outside this one instance, he is normotensive and continues to be monitored off antihypertensive medication to good effect. He currently remains on a semi-annual follow-up schedule.

Discussion

This case highlights the challenges that can arise during the evaluation of secretory AGNs. There was primary concern for a possible ACTH-producing pheochromocytoma, which is a known precipitator of an ACTH-dependent hypercortisolemic state. This suspicion was derived from a myriad of variables. Namely, the presence of high urinary free cortisol with concomitant lack of endogenous cortisol suppression during dexamethasone suppression testing, CT findings of an adrenal mass with relatively elevated HU, the patient's lack of DHEA-S suppression, hypertension, as well as clinically relevant symptoms of anxiety and diaphoresis. However, the findings of normal plasma metanephrines and high-normal normetanephrines indicated that if the underlying pathologic process was truly a pheochromocytoma, it was likely small and nonsecretory in nature. Therefore, there remained some degree of diagnostic ambiguity that stemmed from the relative discordance between the patient's clinical presentation (as well as radiographic findings) and the ensuing biochemical work-up.

AGN is a rare, mature, fully differentiated neoplasm of the sympathetic nervous system, representing less than 5% of adrenal tumors and 21% of ganglioneuromas [3]. This benign tumor arises from neural crest cells, or multipotent stem cells located beside the neural tube proximal to the epidermal layer. Post neurulation, these cells migrate and differentiate into either chromaffin cells or preganglionic sympathetic fibers within the adrenal medulla. Preganglionic fibers function analogously to ganglions by releasing acetylcholine, which stimulates chromaffin cells to release catecholamines. However, chromaffin cells, unlike typical postganglionic sympathetic neurons, release neurotransmitters directly into the bloodstream rather than onto target organs, amplifying the effects of direct sympathetic nerve stimulation by reaching multiple organs simultaneously. Thus, the medulla is considered modified neural tissue [4, 5].

While pheochromocytomas and AGNs both arise from neural crest cells, their specific origins and cellular compositions remain distinct [6]. Pheochromocytomas are localized to the adrenal medulla, arising from chromaffin cells derived from the neural crest and producing catecholamines. AGNs originate directly from neural crest cells themselves, but progress into tumors of mature ganglion cells, Schwann cells, and nerve fibers. They are also located within the medulla (Fig. 2) [6].

While pheochromocytoma is a rare type of neuroendocrine malignancy, it is well-established that in certain instances it is associated with ectopic ACTH production and subsequent CS. This phenomenon was documented as early as 1964. Furthermore, it has been estimated that about 5% of ectopic ACTH-syndrome cases are due to ACTH-secreting pheochromocytomas [7]. It has also been noted that concomitant pheochromocytoma and CS pose a compounding risk of various severe complications for affected patients. Therefore,

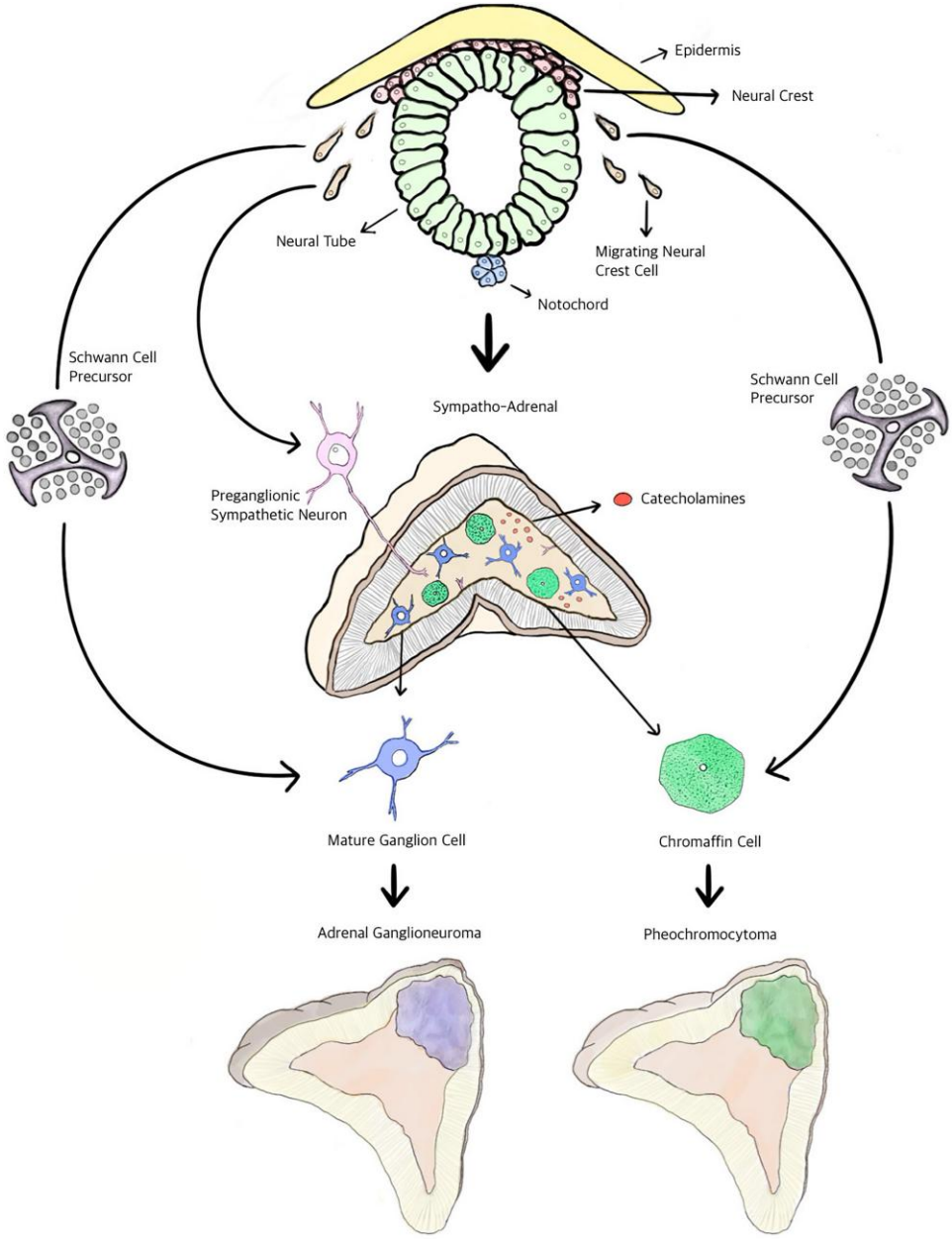

Figure 2. Diagram demonstrating the differentiation of neural crest cells into adrenal medullary cells during embryogenesis. Neural crest progenitor cells differentiate into Schwann cell precursor cells, which further differentiate into mature ganglion cells and chromaffin cells. Both of these neural-derived cell types constitute the adrenal medulla. Adrenal ganglioneuromas are primarily composed of mature ganglion cells, while pheochromocytomas are tumors of chromaffin cells.

it is encouraged that thoughtful consideration of ectopic ACTH-secreting pheochromocytomas be incorporated within the broader evaluation of ACTH-dependent CS [8].

In addition, it is very uncommon for ganglioneuromas to demonstrate secretory properties; however, in rare cases such as the one described herein, they may be endocrinologically active and demonstrate some degree of hormone secretion [1]. Burns et al [9] reported fewer than 10 documented instances of hormone-secreting pure AGNs (as of 2020). In those cases, the implicated hormones included a variable combination of dopamine, norepinephrine, normetanephrine, and even testosterone. Furthermore, in these reports, it was common to see a primary concern for underlying pheochromocytoma leading up to a diagnostic histopathologic examination demonstrating an alternative finding of secretory AGN.

Moreover, composite pheochromocytoma (CP) is a condition characterized by the coexistence of an endocrine tumor (typically pheochromocytoma or paraganglioma) and a neurogenic tumor (usually ganglioneuroma but occasionally ganglioneuroblastoma, neuroblastoma, or schwannoma) [6, 10-12]. There are fewer than 100 reported cases of CP in the literature. Of the two components of CP, only the pheochromocytoma has been noted as secretory, evidenced by increased levels of either urinary or free plasma epinephrine and norepinephrine in most patients. The neurogenic component in CP has never been reported to secrete hormones [6, 10-12].

There is one previous report of CS due to a pure AGN as well as a separate but related case of ACTH-producing para aortic ganglioneuroma leading to ACTH-dependent CS [13, 14]. Therefore, to our knowledge, we are presenting the

second documented instance of an ACTH-producing pure AGN causing ACTH-dependent CS.

The underlying pathogenesis of the atypical secretory characteristics of this patient's AGN remains unclear. Furthermore, regarding ganglioneuromas overall, there remains a global lack of understanding surrounding their underlying biology [2]. However, given the knowledge that ganglioneuromas are derivatives of multipotent neural crest cells, we hypothesize that this neoplasm may retain or reacquire the ability to express hormonal functions associated with neuroendocrine cells, including ACTH production. This idea of phenotypic plasticity is supported by DeLellis et al [15], who described how neuroendocrine gene activation and expression in diverse cell types could potentially be modulated by various microenvironmental influences at different points during neoplastic development. One such microenvironmental influence is hypoxia and the subsequent upregulation of the transcription factor hypoxia-inducible factor 2 α, which appears to contribute to the development of an aggressive and undifferentiated stem-cell like phenotype in certain neural crest–derived adrenal neoplasms [4, 16]. An additional microenvironmental influence in the adrenal medulla is corticotropin-releasing hormone (CRH). Medullary chromaffin cells have the ability to produce ACTH when activated by CRH present in the medulla [17]. It is therefore plausible that ganglioneuromas specifically located in the adrenal medulla are stimulated by local CRH to produce and secrete ACTH. We herein present a rare case of an ACTH-secreting adrenal ganglioneuroma leading to a mild hypercortisolemic state manifested solely by hypertension that resolved postoperatively. It is possible that there are other cases of ACTH-secreting adrenal ganglioneuromas in which hormonal secretion is subtle and underappreciated.

Learning Points

- AGNs, while typically benign and nonsecretory, are capable of demonstrating secretory properties with clinical presentations that vary based on the hormone(s) involved.
- Secretory AGNs can often mimic other adrenal pathologies, particularly pheochromocytomas, and lead to difficulties in diagnosis.
- Definitive diagnosis of AGNs requires histopathologic assessment.
- In cases of ACTH-dependent hypercortisolism with evidence of an adrenal lesion, consideration of secretory AGN is recommended.

Contributors

All authors made individual contributions to authorship. A.C.L. was involved in the diagnosis and treatment of the patient as well as the gathering of data and writing of the manuscript. D.A. and P.V. were involved in manuscript writing and submission. A.K. was involved in interpretation of data, hypothesis generation, and manuscript writing. G.F.R. was involved in surgical management and editing of the manuscript. All authors were involved in the case discussion. All authors reviewed and approved the manuscript draft.

Funding

No public or commercial funding.

Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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