Disclaimer:
The view(s) expressed herein are those of the author(s) and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, or the Department of Defense or the U.S. Government.

Title
Adrenal adenoma anarchy. A case of an ACTH-secreting pheochromocytoma.

Authors: Michelle N. Lee, MD[1]; WingYee Wan, MD[1]; Dianna Chormanski, MD[2]; Maria I. Kravchenko, MD[1]

[1]Department of Medicine, Department of Endocrinology, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234
[2]Department of Pathology, San Antonio Military Medical Center, 3551 Roger Brooke Drive, JBSA Fort Sam Houston, TX 78234
Michelle.n.lee7.mil@mail.mil

Abstract
Introduction: Pheochromocytomas are rare neuroendocrine tumors that arise from sympathetic adrenomedullary chromaffin tissue. Depending on the amount of catecholamines they secrete, they have variable presentations. There have been reported cases of adrenocorticotrophic (ACTH) secreting pheochromocytomas that present with severe Cushing syndrome. Here we present a pheochromocytoma with adrenocorticotrophic hormone (ACTH) co-secretion, which due to its rarity and variable presentation, may be a diagnostic challenge.
Presentation: A 64-year-old woman with history of colon cancer presented with new onset diabetes, worsening hot flashes, and hypertension. On CT imaging she had an enlarging right adrenal nodule (1.7cm) with 60 Hounsfield units of attenuation and no PET avidity. Biochemical evaluation showed elevated urinary and plasma metanephrines, elevated plasma cortisol levels despite dexamethasone suppression, elevated late-night salivary cortisol, and high normal adrenocorticotrophic hormone. The patient underwent laproscopic right adrenalectomy, and pathology confirmed pheochromocytoma. Her lab abnormalities and symptoms of hot flashes and hypertension improved postoperatively.
Conclusion: This case demonstrates an unusual ACTH-secreting pheochromocytoma with subtle presentation and highlights the importance of obtaining a complete biochemical evaluation of incidental adrenal adenomas.

Key words: pheochromocytoma, ACTH co-secretion

Introduction:
Pheochromocytomas are rare neuroendocrine tumors that arise from sympathetic adrenomedullary chromaffin tissue. Presentations are variable depending on the amount of catecholamine secretion. Classically, patients present with the nonspecific triad of palpitations, headaches, and/or sweating, although recent studies have found only 17% of patients diagnosed with pheochromocytoma to present classically.[1] Another study by Gruber *et al*. reported 61% of pheochromocytomas to be asymptomatic and diagnosed on incidental imaging. Due to its

47 nonspecific presentation, a high level of suspicion is needed for the diagnosis of a
48 pheochromocytoma and rare ACTH-producing pheochromocytomas may be a diagnostic
49 challenge. Patients can present with severe Cushing Syndrome (CS), resistant hypertension,
50 diabetes mellitus, and hypokalemia. Due to the high prevalence of obesity, metabolic syndrome,
51 diabetes mellitus and hypertension, and the potentially subtle physical findings associated with
52 cortisol excess, the diagnosis of CS alone can be challenging. Here we report how an ACTH-
53 secreting pheochromocytoma, being a rarity, can cause a delay in diagnosis and treatment.
54
55 **Case Presentation:**
56 A 64-year-old woman with a history of hypertension, obesity, diabetes mellitus, and ileocecal
57 carcinoma status-post right hemicolectomy with ileal resection was evaluated in 2018 for hot
58 flashes, worsening hypertension, and new-onset diabetes in association with an enlarging adrenal
59 nodule. Physical exam was notable for an elevated blood pressure to 165/93 but did not reveal
60 abdominal striae, central obesity, or hirsutism. She had a history of a 1.3 cm right adrenal nodule
61 on CT abdomen/pelvis as early as 2012, found incidentally on evaluation for her colorectal
62 cancer. It was not further evaluated until 2013, at which time it was stable in size (Figure 1). Her
63 hormonal workup in 2013 was remarkable for elevated urine metanephrines to less than twice the
64 upper limit of normal, an appropriately suppressed cortisol level on her overnight dexamethasone
65 suppression test (DST), and normal renin and aldosterone levels (Table 1). The patient was again
66 lost to follow-up for several years and continued to have poorly controlled hypertension and
67 worsening diabetes mellitus. On surveillance CT in October 2018, the adrenal nodule was noted
68 to have grown to 1.7 cm in size with 60 Hounsfield units of attenuation and no PET avidity
69 (Figure 2). Repeat laboratory evaluation revealed elevated urinary metanephrines and elevated
70 serum metanephrines, now three to four times the upper limit of normal (free metanephrines
71 403pg/mL [0-62], free normetanephrine 482mcg/mL [0-145]). She now had a non-suppressed
72 cortisol on DST (cortisol 11.4mcg/dL [0-3], dexamethasone 226 ng/dL), two elevated late night
73 salivary cortisol readings (0.173 mcg/dL, 0.097 mcg/dL [0-0.090]), and a high-normal ACTH
74 level of 45.62pg/mL (6-50) (Table 1). The patient's serum potassium was consistently normal.
75
76 The patient was diagnosed with an ACTH-producing pheochromocytoma and due to the lack of
77 PET avidity there was less concern for colon cancer metastasis. Doxazosin and a high salt diet
78 were initiated prior to undergoing an uncomplicated laparoscopic right adrenalectomy in May
79 2019. Pathology confirmed pheochromocytoma with low mitotic index and positive for
80 synaptophysin and chromogranin. Immunohistochemical staining confirmed ectopic
81 hypersecretion of ACTH (Figure 3a, b).
82
83 Her hot flashes, hypertension, and diabetes significantly improved following surgery, and she no
84 longer required doxazosin or insulin. Repeat laboratory testing showed normalization of her
85 cortisol on DST (cortisol 0.4 mcg/dL, dexamethasone 240 ng/dL), normal ACTH (42 pg/mL),
86 normal metanephrine levels (35 pg/mL), and only slightly elevated normetanephrine levels (189
87 pg/mL), deemed normal for her age and history of essential hypertension.
88
89 **Discussion:**
90 Pheochromocytomas, although rare, are becoming more common due to incidental detection on
91 CT. Gruber *et al*. identified that incidental pheochromocytomas were typically found in older
92 patients, with fewer symptoms and with a smaller degree in elevation of urine and serum

metanephrines compared to those diagnosed based on symptoms. Incidentally discovered pheochromocytomas were also found to require less cumulative phenoxybenzamine compared to those with symptoms.[2]

This patient's pheochromocytoma was initially identified as an incidentaloma on multiple CT scans for surveillance of her colon cancer. Her symptoms of worsening hypertension and night sweats were not the classic triad presentation for a pheochromocytoma, which may be due to having only moderate catecholamine secretion. There was also a concern for subclinical Cushing's syndrome based on her non-suppressed cortisol on DST and elevated late night salivary cortisol levels.

ACTH-producing pheochromocytomas are rarely diagnosed, comprising approximately 5% of cases of ectopic ACTH syndrome, with less than 100 reported cases.[3] It more commonly presents in women and unilaterally. Patients will typically present with severe CS with diabetes mellitus and significant hypokalemia, and will less likely present with catecholamine excess.[4] The diagnosis can sometimes be challenging as symptoms are nonspecific, although they typically present less insidiously than classic Cushing's syndrome. Our patient's presentation was more insidious, without clinical symptoms or signs of Cushing's syndrome or hypokalemia that would suggest a secondary cause of her hypertension and diabetes mellitus. Hypertension and intermittent sweating or hot flashes were her only symptoms of catecholamine excess.

Patients with ectopic ACTH syndrome can present with variable ACTH as well, ranging from normal levels, as seen in our patient, to over 200 pg/ml.[3, 5] Although her preoperative ACTH was within normal limits, this was inappropriate in the setting of her hypercortisolism. Repeat ACTH postoperatively was slightly improved and appropriate for a preserved hypothalamus-pituitary-adrenal axis. Due to already having a diagnosis of a right pheochromocytoma, the decision to undergo an adrenalectomy was made prior to any further workup for hypercortisolism. The normal postoperative suppression of cortisol and positive ACTH staining of the tumor confirmed that her pheochromocytoma was the ectopic source. If further workup was necessary—for example, ACTH staining was negative—the tumor could have been stained for CRH to assess for ectopic secretion. Additionally, a high dose DST or CRH stimulation test could assist in differentiating a pituitary from an ectopic source. High dose DST is noted to have only 76.5% accuracy, as 20-30% of ectopic ACTH-producing tumors have functioning glucocorticoid receptors that can still suppress ACTH production.[4]

It is important to treat the excess catecholamines and cortisol prior to surgery in ACTH-producing pheochromocytomas. Patients are typically treated with an alpha blocker in addition to other antihypertensives to control their hypertension. In the case of the hypercortisolism, treatment is dependent on the severity and may include metyrapone and/or ketoconazole to directly prevent further production of cortisol, potassium supplementation to correct hypokalemia, and insulin to control hyperglycemia. Medical therapies are usually tapered and discontinued following adrenalectomy. Patients with a unilateral adrenalectomy will typically still require a short course of steroids.[3] As our patient did not present with overt Cushing's syndrome, preoperative ketoconazole was not deemed necessary.

138 Unlike other ectopic ACTH-producing tumors, pheochromocytomas are usually benign and
139 cured following unilateral adrenalectomy. Many other tumors that have been associated with
140 ectopic ACTH production are usually metastatic at time of diagnosis and may require palliative
141 bilateral adrenalectomy.[5, 6]
142
143 **Acknowledgements:** none
144
145 **Abbreviations:**
146 ACTH adrenocorticotrophic hormone
147 CS Cushing syndrome
148 DST dexamethasone suppression test
149 CRH corticotropin-releasing hormone
150
151
152 **Disclosure:**
153 The authors have no multiplicity of interest to disclose.

154

155 **References:**
156 1. Falhammar H, Kjellman M, Calissendorff J. Initial clinical presentation and spectrum of
157 pheochromocytoma: a study of 94 cases from a single center. *Endocr Connect*.
158 2018;7(1):186–192.
159 2. Gruber L, Hartman R, Thompson G, McKenzie T, et al. Pheochromocytoma
160 Characteristics and Behaviors Differ Depending on Method of Discovery. *Journal of*
161 *Clinical Endocrinology and Metabolism.* 2019; 104(5): 1386-1393.
162 3. Gabi J, Milhem M, Tovar Y, Karem E, et al. Severe cushing syndrome due to an ACTH-
163 producing pheochromocytoma: A case presentation and review of the literature. *Journal*
164 *of the Endocrine Society*. 2018; 2(7): 621-630.
165 4. Nijhoff M, Dekkers O, Vleming L, et al. ACTH-producing pheochromocytoma: clinical
166 considerations and concise review of the literature. *European Journal of Internal*
167 *Medicine.* 2009; 20: 682-685.
168 5. Salgado L, Fragoso M, Knoepfelmacher M, et al. Ectopic ACTH syndrome: our
169 experience with 25 cases. *European Journal of Endocrinology.* 2006; 155: 725-733.
170 6. Chen H, Doppman J, Chrousos G, et al. Adrenocorticotropic hormone-secreting
171 pheochromocytomas: The exception to the rule. *Surgery.* 1995; 118(6): 988-995.
172

173 **Supplemental Materials**

174

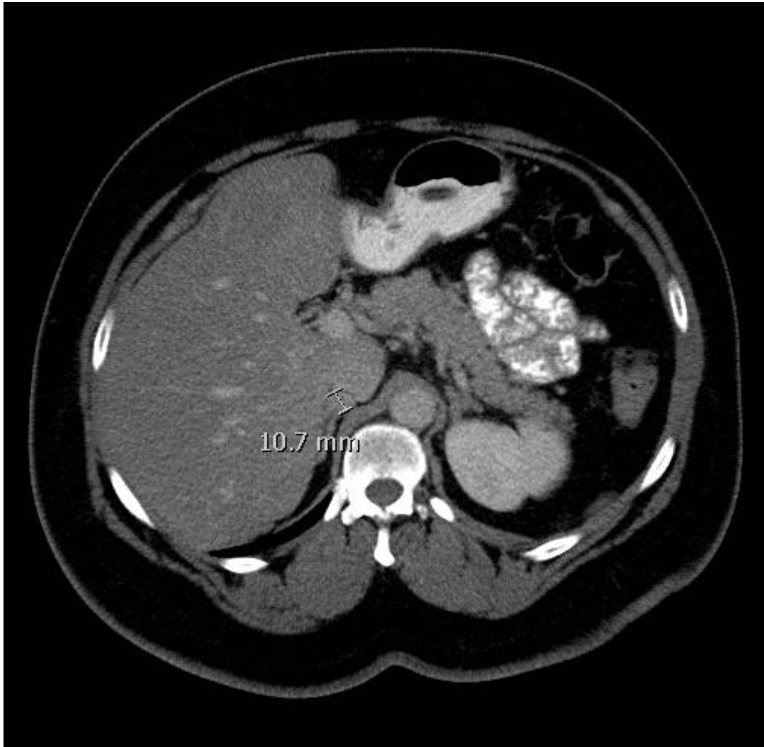
175 **Table 1 – Hormonal evaluation**

	Initial screening Jul2013	Repeat screening Nov2018	Jan2019	Jun2019 (1 month postoperative)
AM Cortisol with 1mg overnight DST	1.2 mcg/dL	7.3mcg/dL	11.4mcg/dL	0.4mcg/dL

Late night salivary cortisol at 0300 (0-0.090 mcg/dL)			0.175mcg/dL, 0.173mcg/dL, 0.097 mcg/dL	
24hr urinary cortisol (36-137 mcg/24hr)			89.0 mcg/24hr	
Adrenocorticotrophic hormone (ACTH) (6.00-50 pg/mL)			45.62 pg/mL	
24hr urinary metanephrines (74-297 mcg/24hr)	505 mcg/24hr	864 mcg/24hr		
24hr urinary normetanephrine (105-354 mcg/24hr)	434 mcg/24hr	690 mcg/24hr		
24hr urinary metanephrines, total (179-651 mcg/24hr)	939 mcg/24hr	1554 mcg/24hr		
Plasma free metanephrine (0-62 pg/mL)	-	403 pg/mL	199 pg/mL	35 pg/mL
Plasma free normetanephrine (0-145 pg/mL)	-	482 pg/mL	176 pg/mL	189 pg/mL
Plasma renin (0.25-5.82 ng/mL/h)	1.77 ng/mL/h	1.121 ng/mL/h	-	-
Plasma aldosterone (0-30 ng/dL)	13 ng/dL	10.6 ng/dL	-	-

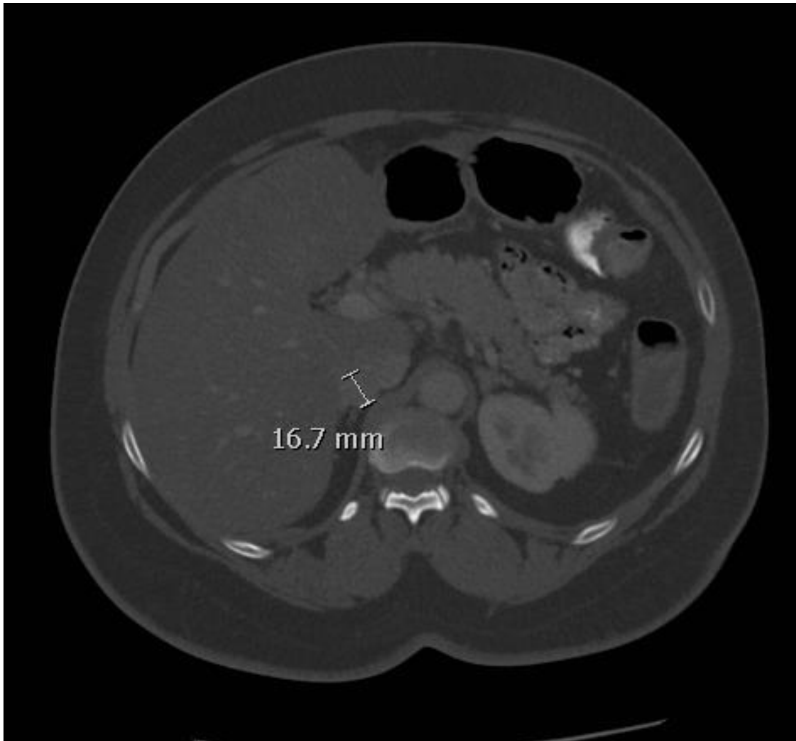
Figure 1: Initial CT imaging of incidental right adrenal nodule measuring 1.1 cm.

186



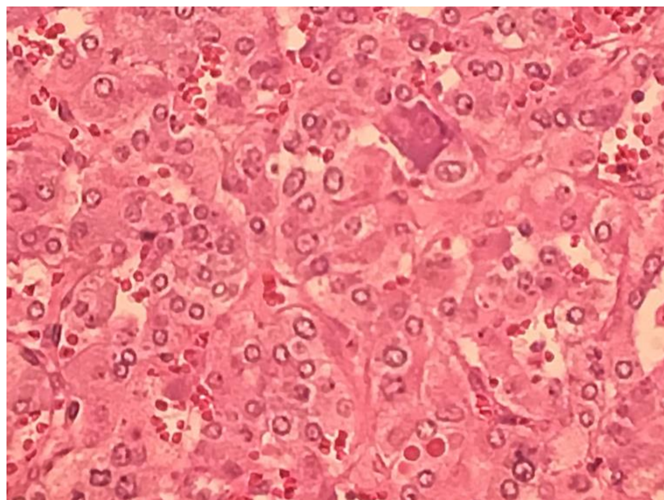
187

188 **Figure 2:** Follow-up CT noting an increase in size of the right adrenal nodule (1.7 cm) with 60
189 Hounsfield units of attenuation (right)



190

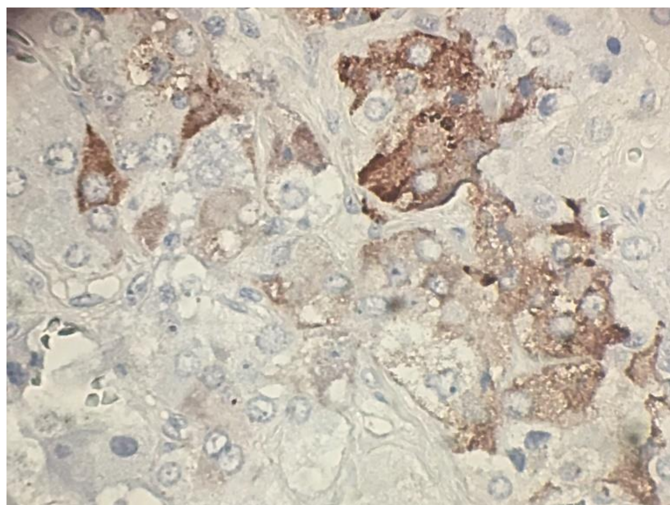
191 **Figure 3a:** Hematoxylin and eosin stain demonstrating polygonal tumor cells with vesicular
192 nuclei and some prominent nucleoli growing in a nested pattern.



201

202

203 **Figure 3b:** Immunohistochemical stain for adrenocorticotrophic hormone demonstrating tumor
204 cells with patchy positive staining (brown).



205

206

207