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A Rare Case of Metastatic Adrenocorticotrophic Hormone – Secreting Pancreatic Neuroendocrine Tumor Causing Ectopic Cushing Syndrome in a 46-Year-Old Woman

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Jessica Y. Huang
CDEF 2 Nikitha A. Cherayil
ACE 1 Paul Boyd
BCD 3 Maher Ali
ABCDEF 1 Shazia Samanani

1 Department of Medicine, The George Washington University, Washington, DC, USA
2 Department of Internal Medicine, The George Washington University, Washington, DC, USA
3 Department of Pathology, The George Washington University, Washington, DC, USA

Corresponding Author: Shazia Samanani, e-mial: ssamanani@mfa.gwu.edu
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Patient: Female, 46-year-old
Final Diagnosis: Metastatic adrenocorticotrophic hormone – secreting pancreatic neuroendocrine tumor
Symptoms: Acne • fatigue • hair loss • hypertension • insomnia • weight gain
Clinical Procedure: —
Specialty: Endocrinology and Metabolic • General and Internal Medicine

Objective: Rare disease

Background: Adrenocorticotrophic hormone (ACTH)-secreting pancreatic neuroendocrine tumors (pNETs) are rare and poorly understood entities. Only 1-2% of pancreatic neoplasms are pNETs, and even fewer are hormone-secreting. They can present indolently or with overt Cushing syndrome. Their diagnosis involves complex multi-modal imaging and laboratory evaluation. Management includes medications, such as somatostatin analogs and ketoconazole, as well as surgical resection for definitive treatment. This report describes a 46-year-old woman who presented with overt Cushing syndrome and was ultimately diagnosed with a pNET.

Case Report: This patient's initial symptoms and laboratory testing were consistent with Cushing syndrome. A high-dose dexamethasone suppression test suggested ectopic ACTH production, and magnetic resonance imaging (MRI) of the brain showed a pituitary microadenoma. However, computed tomography (CT) of the abdomen and endoscopic ultrasound-guided biopsy with immunohistochemistry confirmed a pancreatic mass as the source of ACTH production with potential hepatic metastasis. Her Cushing syndrome was managed with ketoconazole and octreotide. Subsequently, >99% of the pNET was surgically removed, resulting in reversal of her Cushing syndrome. Currently, she is being monitored closely for recurrence.

Conclusions: Our management of this ACTH-secreting pNET highlights the complexities of diagnosis and multidisciplinary treatment options, which are underrepresented in the current literature on this rare entity. This case emphasizes the challenges in evaluation, including the importance of early and precise diagnosis in the face of potential confounders.

Keywords: Endocrine Gland Neoplasms • Pancreatic Neoplasms • Neuroendocrine Tumors • Cushing Syndrome • ACTH Syndrome, Ectopic

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/945653

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Introduction

Ectopic adrenocorticotropic hormone (ACTH) syndrome (or ectopic Cushing syndrome) is a condition caused by ACTH-secreting tumors, or neuroendocrine tumors (NETs), outside of the pituitary gland [1]. Ectopic ACTH secretion suppresses central pituitary ACTH production and stimulates the adrenal glands to produce cortisol above physiologic levels, which can manifest as Cushing syndrome. Ectopic ACTH production is clinically differentiated from excess central production by use of biochemical testing, imaging, and bilateral inferior petrosal sinus sampling (BIPSS) [2]. ACTH-secreting NETs are typically located in the lungs, thymus, and pancreas [1]. Pancreatic NETs (pNETs) cause a rare, but appreciable, number of ectopic ACTH syndrome cases [1,3]. These tumors are rare; pNETs comprise between 8 and 15% of all NETs, with only around 100 cases of ACTH-secreting pNETs reported to date [2,3].

There are few case reports that describe ACTH-producing metastatic pNETs requiring significant testing due to a confounding mass, several medical therapies, and an extensive surgical procedure to manage the Cushing syndrome caused by the tumor. Here, we report a case of a 46-year-old woman who developed severe Cushing syndrome secondary to a metastatic ACTH-secreting pNET. We describe the diagnosis and successful medical and surgical management of this rare neoplasm that was complicated by a pituitary microadenoma that acted as a confounder.

Case Report

A 46-year-old woman with no past medical history presented with worsening leg swelling, abdominal girth, 50-pound weight gain, acne, hair loss, dyspnea, fatigue, and insomnia over 4 months. Outpatient laboratory test results were significant for elevated AM cortisol of 35.4 µg/dL (normal: 4.5-23.0 µg/dL) and ACTH of 241 pg/mL (normal: 7.2-63.3 pg/mL), and the patient was told to come in for urgent evaluation for new-onset Cushing syndrome. On presentation, her blood pressure was elevated to 160/90. Laboratory test results on admission showed a normal complete blood count with white blood cell count of 9.79×10^3/µL (normal: $4.8\text{-}10.8\times10^3$/µL); hemoglobin (Hb) of 14.1 g/dL (normal: 12-16 g/dL); hematocrit (HCT), 44.6% (normal: 37-47%); and platelets, 199×10^3/µL (normal: $130\text{-}400\times10^3$/µL). The basic metabolic panel showed the following values: sodium, 140 mmol/L (normal: 135-145 mmol/L); potassium, 3.0 mmol/L (normal: 3.5-5 mmol/L); chloride, 97 mmol/L (normal: 95-105 mmol/L); bicarbonate, 33 mmol/L (normal: 22-30 mmol/L); blood urea nitrogen (BUN), 20 mg/dL (normal: 7-17 mg/dL); and creatinine 0.6 mg/dL (normal: 0.7-1.2 mg/dL). Her fasting blood glucose level was elevated to 144 mg/dL (normal: 75-110 mg/dL). Liver function tests were normal, with an alkaline phosphatase of 65 units/L (normal: 40-125 units/L), aspartate aminotransferase (AST) of 22 units/L (normal: 15-50 units/L), and alanine aminotransferase (ALT) of 37 units/L (normal: 10-45 units/L). Thyroid stimulating hormone was 0.375 µIU/mL (normal: 0.4-4.7 µIU/mL), free thyroxine (T4) was 0.7 ng/dL (normal: 0.7-1.8 ng/dL), and free triiodothyronine (T3) was 2.5 pg/mL (normal: 2.8-5.3 pg/dL). Hemoglobin A1c was 7% (normal: <6%).

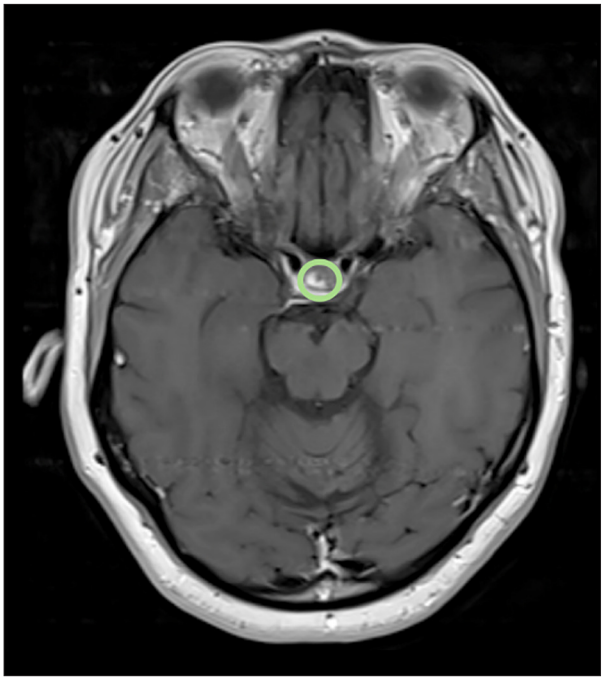

Figure 1. Axial T1 post-contrast image of a right central pituitary gland 6 mm T1 hypointense differentially enhancing lesion with a small focus of T2 hypointensity centrally. No suprasellar extension was evident. No cavernous sinus extension was evident. Midline infundibulum was evident.

Because of the history of elevated ACTH on outpatient laboratory test results, a computed tomography (CT) of the head was ordered to evaluate for a pituitary mass. This was negative, so magnetic resonance imaging (MRI) of the brain was ordered and showed a pituitary microadenoma measuring 6 mm (**Figure 1**), which was initially thought to be the source of her increased ACTH production.

The patient's ACTH level was 254 pg/mL and her initial AM serum cortisol level was 42.1 µg/dL with a max of 80 µg/dL during her admission (normal: 4.5-23.0 µg/dL) (**Table 1**). A low dose 1 mg overnight dexamethasone suppression test produced a cortisol level of 42.7 µg/dL showing unsuppressed AM cortisol. Despite this, cortisol levels remained elevated to 80.3 µg/dL after the 8 mg high-dose dexamethasone suppression test, suggestive of an ectopic source.

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Table 1. Summary of the patient's notable biochemical markers in relation to her day of admission and relevant treatments.

Hospital day	Cortisol level (µg/dL)	ACTH Llevel (mg/mL)	Therapeutic changes
0	42.1	254	
6	63.9		
7	80.3		
10			Ketoconazole started, 200 mg twice daily
11	48.2		
13			Ketoconazole increased to 600 mg every 6 hours
14	39.6	140	
15	15.7		
17	28.6		Octreotide started, 50 µg every 6 hours
18	19.3		
19 (pre-op)	18	150	Steroid replacement started, operative (Whipple) day
20 (post-op)	6.38	19.8	Ketoconazole and octreotide stopped
22	2.42	23	
25	7.28	14.5	

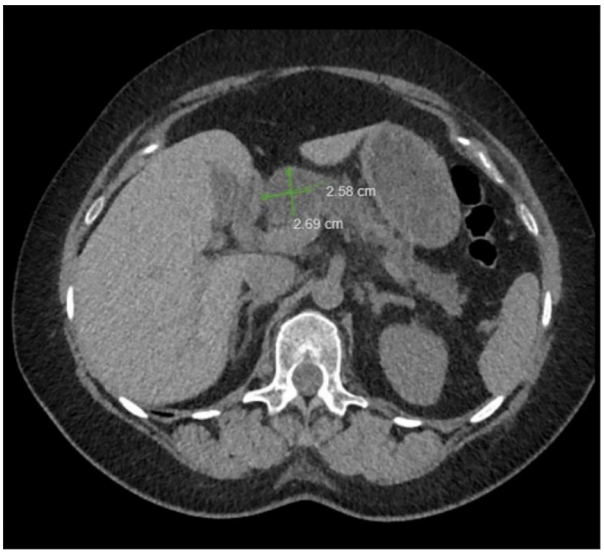

Figure 2. Axial view of a chest CT without contrast which revealed an ill-defined hypodense lesion in the region of the pancreatic head measuring up to 3.4 cm, concerning for malignancy. CT – computed tomography.

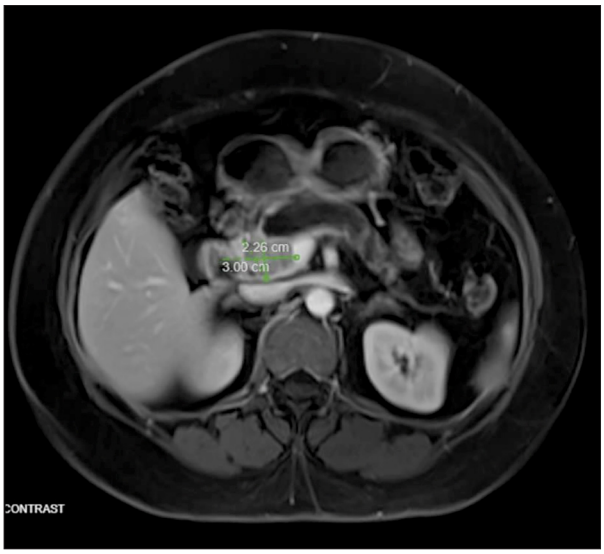

Figure 3. Axial view from an abdominal MRI with and without contrast, that revealed a 3.0×2.3×2.3 cm mass in the pancreatic head causing obstruction and significant dilation of the main pancreatic duct, which was concerning for malignancy. MRI, magnetic resonance imaging.

On day 1 of admission, a CT of the chest was obtained to evaluate the patient's dyspnea. It showed an ill-defined 3.4-cm lesion in the pancreatic head that was concerning for malignancy (**Figure 2**). MRI of the abdomen with pancreas protocol showed a 3-cm pancreatic mass causing obstruction and dilation of the main pancreatic duct, which was worrisome for pancreatic neoplasm, and a small liver lesion, which was concerning for metastatic disease (**Figure 3**). CT of the abdomen confirmed a 3.2-cm pancreatic head mass with encasement of the celiac axis and common hepatic artery as well as upstream pancreatic ductal dilation (**Figure 4**). A small liver lesion was also seen on CT (**Figure 4**). There was concern for multiple endocrine neoplasia syndrome, given the pancreatic and pituitary masses. However, her parathyroid hormone level, calcium level, calcitonin level, plasma metanephrine/normetanephrine levels, adrenal imaging, and thyroid imaging were all

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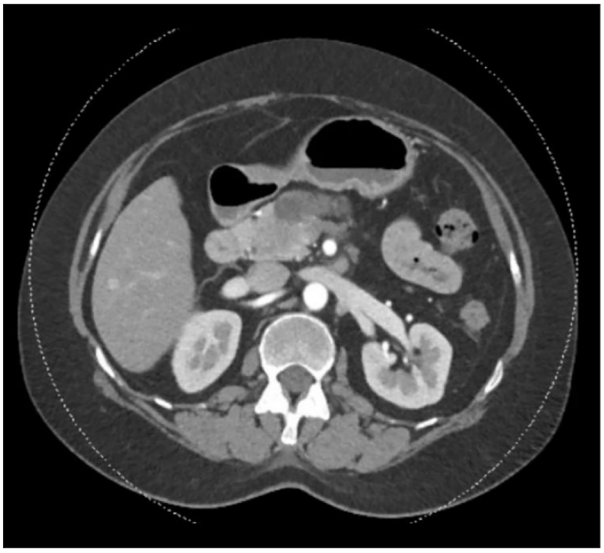

Figure 4. Axial view of the abdominal CT, showing the presence of a 3.2 cm pancreatic head mass with marked upstream pancreatic ductal dilation. CT – computed tomography.

normal. BIPSS was offered to the patient to determine whether the pituitary microadenoma was producing ACTH, but was deferred due to patient preference.

On day 6 of admission, endoscopic ultrasound (EUS)-biopsy of the pancreatic mass confirmed a well-differentiated neuroendocrine tumor, positive for chromogranin, synaptophysin, and ACTH, confirming it as the source of ectopic ACTH production (**Figure 5A-5D**). Ki-67 was low at 8%, suggesting a World Health Organization grade 2 NET (**Figure 5E**). Dotatate-labeled selective somatostatin receptor (SSTR) positron emission tomography (PET) showed an increased uptake in the pancreatic head, thyroid, duodenal wall, and pituitary gland, although it was difficult to distinguish this pituitary uptake from normal physiologic uptake (**Figure 6**). The previously seen liver lesions were too small to be characterized by PET and were noted as indeterminate (**Figure 6**). Once the pathology results were in, the patient was diagnosed with well-differentiated ACTH-secreting pNET causing Cushing syndrome. Her hospital course was also complicated by episodes of mania, psychosis, and hyperactivity that were eventually attributed to her hypercortisolism.

Pending surgical intervention, she was initiated on medical therapy with ketoconazole, initially at a dose of 200 mg twice daily, which was later increased to 600 mg every 6 hours to achieve better symptom control and cortisol level (**Table 1**). Despite improvement in her cortisol levels, she continued to have steroid-induced psychosis, so octreotide 50 µg every 6 hours was started on day 17 of admission. It was not started sooner due to concerns that a prolonged course may overly shrink the tumor making the surgical procedure less successful.

She underwent a successful Whipple procedure on day 19 of admission. Intra-operatively, she was placed on an octreotide drip and was given solumedrol. Seven lymph nodes were assessed and were all negative and one small hepatic metastasis was removed. Histopathology of the resected portion of the pancreas confirmed a well-differentiated neuroendocrine tumor with Ki-67 labeling of at least 60% with a positive margin (**Figure 7**). The surgery resulted in >99% tumor removal as seen on postoperative MRI and there were no known complications postoperatively or in the immediate follow-up period.

Her postoperative laboratory test results showed a decrease of cortisol to 6.389 µg/dL and ACTH of 19.8 pg/mL (**Table 1**). Immediately postoperatively, the octreotide drip and ketoconazole were discontinued, and she was transitioned to hydrocortisone 20 mg at 7: 00 AM and 10 mg at 2: 00 PM. Hydrocortisone was tapered off over the course of 2 weeks. She had immediate postoperative improvement in her hypertension, steroid-induced psychosis, weakness, and hypokalemia. She was discharged home on postoperative day 8.

After discharge, she had monthly follow-up with oncology, endocrinology, and endocrine surgery. Once steroids were tapered off, her cortisol was re-evaluated and found to be 3.4 µg/dL. ACTH stimulation testing showed an initial level of 3.59 µg/dL with a response to 26.3 µg/dL, so steroids were not prescribed. A 6-month postoperative MRI of the abdomen showed an unremarkable remaining portion of the pancreas, and PET scan showed mild diffuse pancreatic uptake thought to be inflammatory.

Discussion

This is a rare case of metastatic ACTH-secreting pNET, resulting in Cushing syndrome. Diagnosis was complicated by the presence of a likely non-functioning pituitary microadenoma, which required a deep understanding of the various locations for aberrant ACTH production and steps in evaluation. As introduced earlier, most documented ACTH-secreting pNET cases do not present a successfully managed complex scenario such as the one detailed here. Some of the current published case reports describe completely resectable tumors that do not require any medical therapy, and some describe tumors that failed treatment despite the use of many medications [4,5]. In other case reports, delays in evaluation and the presence of multiple incidentalomas without focused evaluation resulted in poor outcomes and surgical removal of benign tissues [6,7].

The language surrounding the broader category of neuroendocrine neoplasms has evolved to differentiate between NETs, which are well-differentiated, and pancreatic neuroendocrine carcinomas, which are poorly-differentiated [2]. This terminology has largely replaced the previously used diagnosis of “carcinoid”

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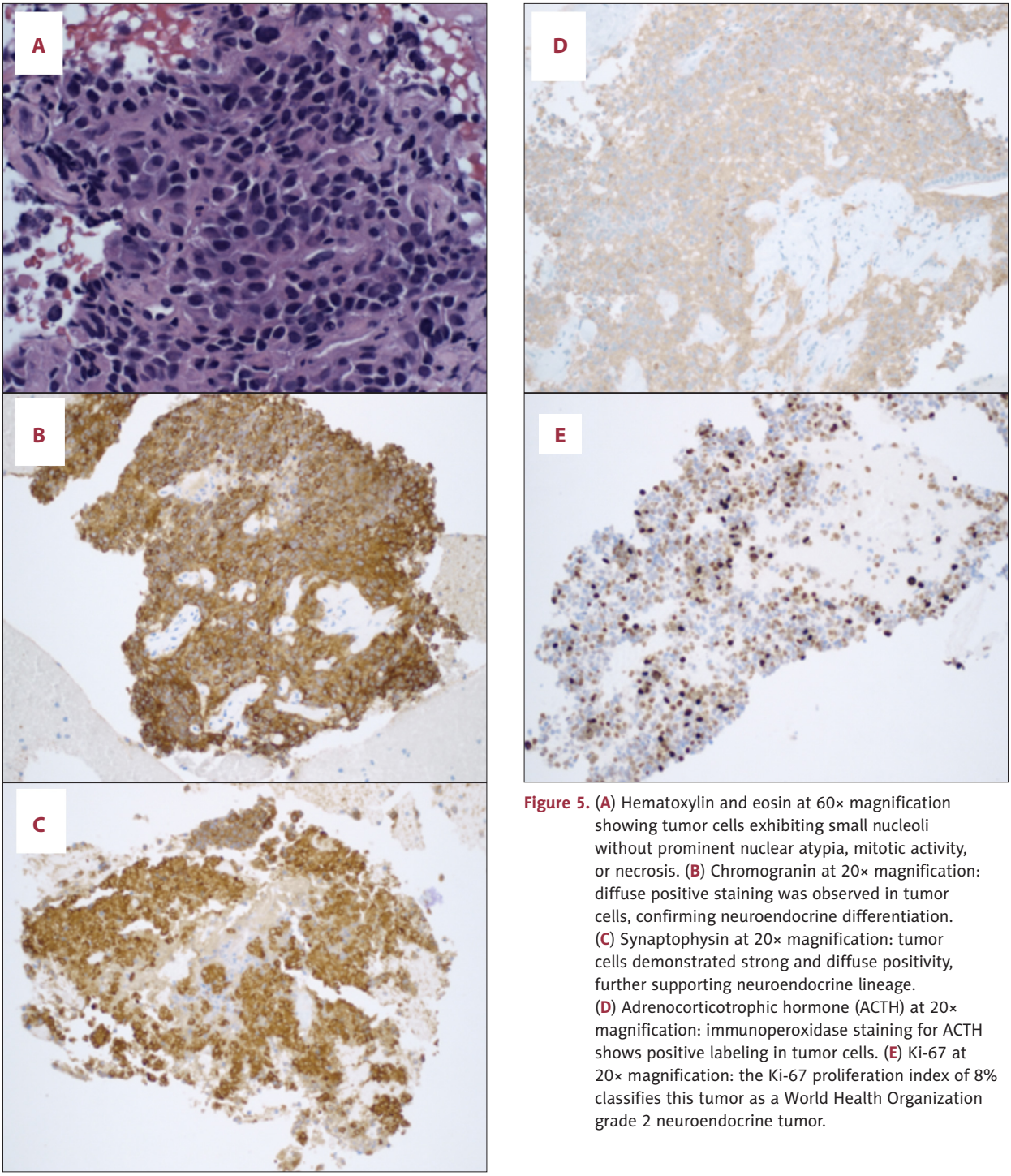

Figure 5. (**A**) Hematoxylin and eosin at 60× magnification showing tumor cells exhibiting small nucleoli without prominent nuclear atypia, mitotic activity, or necrosis. (**B**) Chromogranin at 20× magnification: diffuse positive staining was observed in tumor cells, confirming neuroendocrine differentiation. (**C**) Synaptophysin at 20× magnification: tumor cells demonstrated strong and diffuse positivity, further supporting neuroendocrine lineage. (**D**) Adrenocorticotrophic hormone (ACTH) at 20× magnification: immunoperoxidase staining for ACTH shows positive labeling in tumor cells. (**E**) Ki-67 at 20× magnification: the Ki-67 proliferation index of 8% classifies this tumor as a World Health Organization grade 2 neuroendocrine tumor.

tumors. While neuroendocrine neoplasms can arise in many different sites, we will discuss those arising in the pancreas.

With an incidence of only 1 case per 100 000 patients per year in the US, pNETs are rare, and compromise only 1-2% of all pancreatic neoplasms [8]. Although approximately 80% of pNETs are non-functioning, meaning that they do not secrete hormones, there are rare cases in which they are hormone-secreting, causing symptoms, and are classified as functioning pNETs [9]. Of the functioning pNETs, the majority secrete insulin, gastrin, vasoactive intestinal peptide, glucagon, somatostatin, or serotonin [10]. There are very few cases, a total of about 100 in the English-language literature, that report ACTH secretion causing ectopic ACTH syndrome, as in our case [3].

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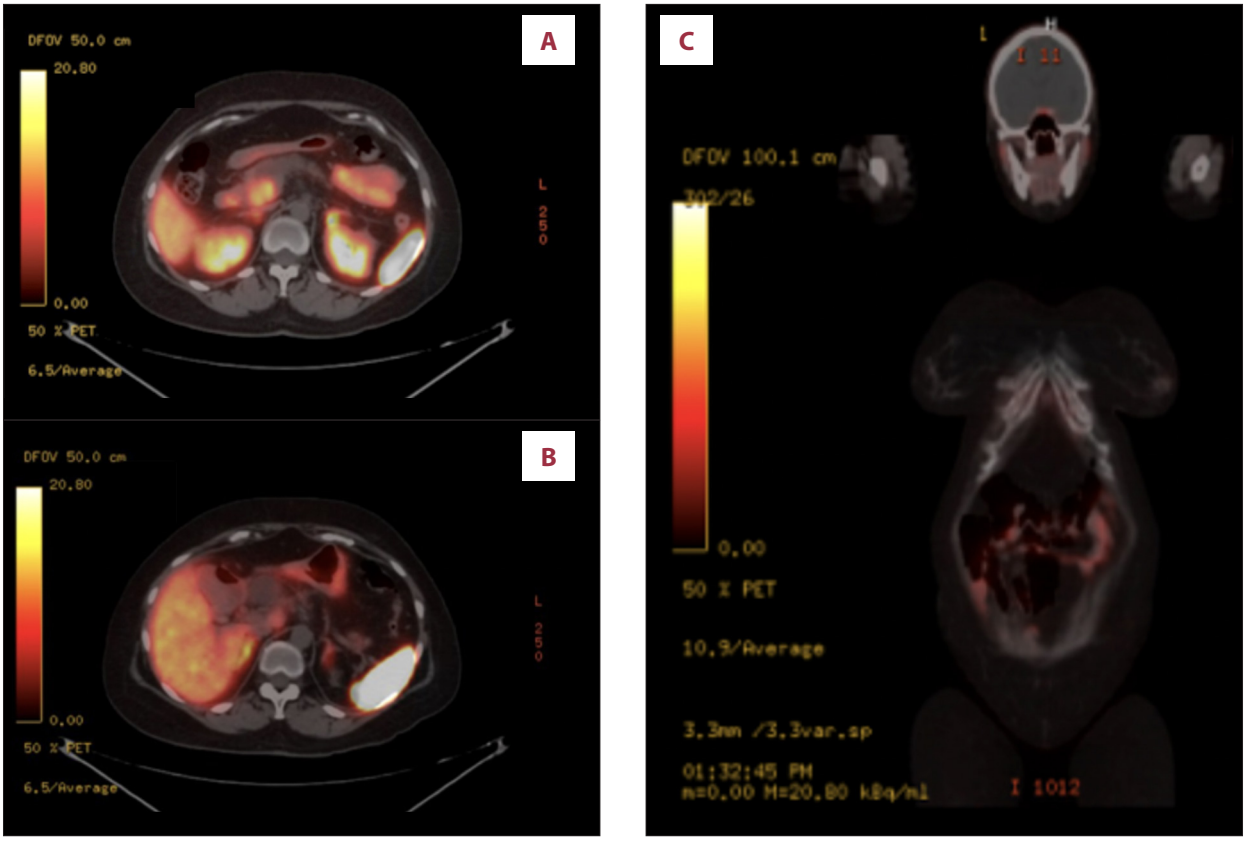

Figure 6. Dotatate-labeled selective somatostatin receptor (SSTR) positron emission tomography (PET) to evaluate primary tumor and metastases. (**A**) Axial cut of the PET scan showing increased uptake in the pancreatic head mass, corresponding to the biopsy-proven pancreatic neuroendocrine tumor. (**B**) Axial cut of the PET scan showing a very small focus of increased uptake in the right hepatic lobe. Metastatic disease cannot be excluded. (**C**) Coronal cut of the PET scan showing uptake in the pituitary gland; however, this may be physiologic.

In those with symptoms and initial lab work suggesting ACTH-dependent Cushing syndrome, low dose dexamethasone suppression test (LDDST) and corticotrophin-releasing hormone (CRH) stimulation test can be used as initial diagnostic tests [2]. In those with suppression on LDDST and stimulation on CRH test, the next step is a pituitary MRI [2]. If it shows a tumor >10 mm, this is diagnostic of Cushing disease [2,11]. However, if there are negative or discordant LDDST and CRH tests in the setting of a pituitary adenoma, the next step is BIPSS, which is the gold standard for differentiating Cushing disease caused by central ACTH production from ectopic ACTH secretion [2,11]. BIPSS is the most accurate procedure to diagnose the cause of excess central ACTH production and is done by sampling ACTH levels at the inferior petrosal sinus [11]. This level is compared with serum ACTH levels to determine whether there is excessive pituitary ACTH production [11]. If BIPSS is negative and does not demonstrate ACTH oversecretion from the pituitary gland, further workup for ectopic ACTH secretion with whole-body imaging is warranted [2].

Imaging should start with CT and MRI, which locate probable primary and metastatic sites for pNETs, helping guide further imaging and evaluation [2,12]. Dotatate-labeled SSTR PET is the advanced imaging technique used to identify NET tumors specifically [12]. SSTR is overexpressed in NETs, so Dotatate-labeled SSTR PET has been shown to have 93% sensitivity and 91% specificity for detection of primary tumors [12]. It is also more successful in identifying metastases compared with conventional CT and MRI [2,12]. Furthermore, the uptake of the tracer is predictive of response to therapy with somatostatin analogs [7,13]. EUS can be useful for functional NETs that are <4 cm, which can go undetected on CT or MRI [12,14]. EUS also offers a nonoperative option for histopathologic diagnosis [15].

Elevations of certain non-hormonal biomarkers, such as chromogranin A and pancreatic polypeptide, have been associated with NETs; however, they have variable sensitivity and specificity in diagnosis due to their elevations in other malignancies and inflammatory conditions [10]. Thus, they are better used as markers to monitor response to treatment and recurrence [10]. The hormones that are produced by NETs, such as ACTH in this case, provide more utility in diagnosis, treatment-response, and surveillance in conjunction with imaging [10].

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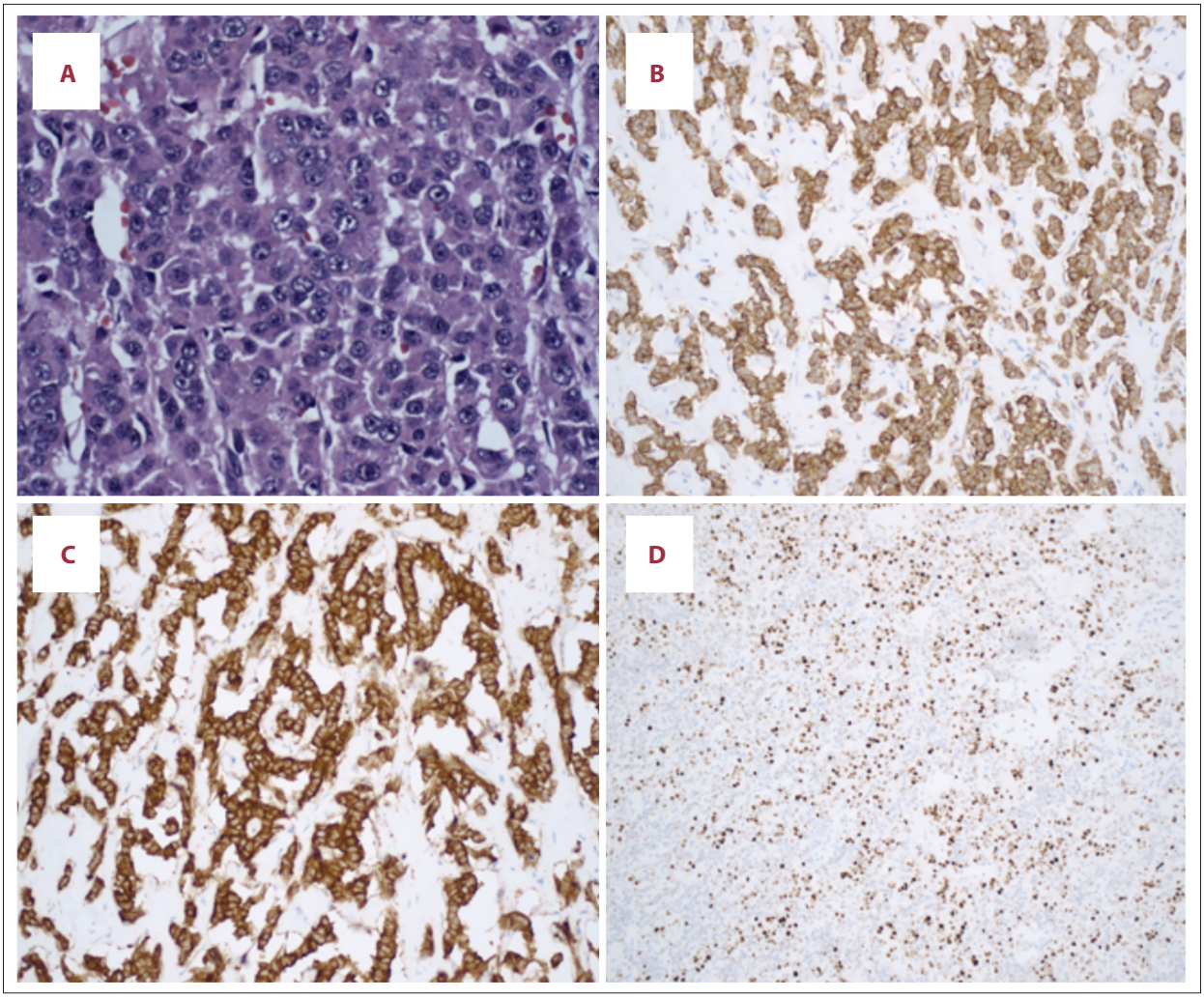

Figure 7. (**A**) Hematoxylin and eosin at 60× magnification: tumor cells exhibit large vesicular nuclei with prominent nucleoli. (**B**) Chromogranin at 20× magnification: diffuse and strong positive staining is observed in tumor cells, confirming neuroendocrine differentiation. (**C**) Synaptophysin at 20× magnification: tumor cells are strongly positive for synaptophysin. (**D**) Ki-67 at 20× magnification: the Ki-67 labeling index is at least 60%, indicating a high proliferative rate.

In our patient's case, she presented with symptoms of Cushing syndrome, and laboratory test results confirmed ACTH-dependent pathophysiology. Initial diagnosis was complicated by a pituitary mass found on brain imaging. However, dexamethasone suppression testing revealed the mass as a confounder, so workup for an ectopic source was pursued. In our case, BIPSS was deferred due to patient preference. Ultimately, CT and MRI found a pancreatic mass confirmed by Dotatate-labeled SSTR PET. EUS-guided biopsy of the pancreatic mass with ACTH staining confirmed it as the source of the ectopic ACTH production.

Ketoconazole is a mainstay treatment of symptomatic Cushing syndrome because it inhibits the excess production of cortisol [16]. It works by blocking several CYP enzymes involved in adrenal steroidogenesis [16]. It most effectively reduces cortisol synthesis through blocking CYP17A1 17a-hydroxylase activity; however, it also has inhibitory effects on 11B-hydroxylase and 18-hydroxylase, inhibiting cortisol and aldosterone synthesis [16]. Dosing starts at 400 to 600 mg/day in 2 or 3 divided doses and can be increased to a maximum of 1200 mg/day in 2 or 3 divided doses [16]. It is important to keep in mind that ketoconazole requires acidity to be absorbed, so proton pump inhibitors must be discontinued [16]. Other adverse effects include hepatotoxicity, requiring frequent liver function monitoring; prolongation of QT interval; and inhibition of CYP3A4 [16,17]. Overall, ketoconazole is a well-tolerated and effective drug in suppressing hypercortisolism that can be used pre-operatively, as in our patient, as well as for long-term management [16,17].

Somatostatin analogs (SSAs) are often used in pNETs as first-line therapy to slow disease progression, manage symptoms,

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and control overall tumor growth [18,19,20]. Some studies have also demonstrated a clinical and biochemical benefit for patients treated with SSAs [19]. The most commonly used SSA is octreotide followed by lanreotide [9,10]. For our patient, SSAs were used due to the uptake on her Dotatate-labeled SSTR PET scan, and octreotide was favored due to availability. SSA therapy is currently first-line therapy for functional pNETs [9,10,15]. SSAs bind to somatostatin receptors on tumor cells resulting in a direct antiproliferative effect while also engaging in systemic, indirect antiproliferative activity by inhibiting angiogenesis and secretion of growth factors [18,20]. In particular, lanreotide and octreotide inhibit peptide secretion from pNETs primarily through the SSTR2 and SSTR5 receptors, which have been found to be expressed on 80% of pNETs [19]. A newer SSA, pasireotide, targets a broader range of SSTR receptors, most notably SSTR1, 2, 3, and 5 [20]. While an in vivo octreotide loading test or immunostaining for SSTR2 or SSTR5 is not always done on biopsies, The North American Neuroendocrine Tumor Society recommends somatostatin analogs as first-line treatment for patients with advanced pNETs to slow disease progression given its tolerability [9,15]. The CLARINET study demonstrated the rate of progression of pNETs to be 42.8% in those who received an SSA vs 63.3% in the placebo group [19]. With SSAs, patients are also able to achieve long-term suppression of ACTH and cortisol levels as well as reduction in symptoms [21].

In addition to SSAs, cabergoline has also been used to suppress ACTH secretion in ectopic ACTH syndrome [21,22]. Cabergoline is a dopamine receptor agonist usually used off-label for Cushing disease when there is ACTH hypersecretion from a pituitary adenoma [21,22]. Its use in ectopic ACTH syndrome is lesser known; however, some cases show suppression of ACTH, suggesting the presence of dopamine receptors in these ectopic sources [21,22].

EUS-guided radiofrequency ablation is also an emerging therapeutic option being assessed for patients with pNETs [14,23]. Its therapeutic mechanism occurs through induced tumor mass thermal necrosis [14,23]. It has been successfully used in patients with insulinomas and non-functional pNETs [14,23]. It has been used in patients who declined surgery or were not candidates for surgery [14,23].

Peptide receptor radionuclide therapy (PRRT) has also shown some benefit in treating pNETs as a second-line option and is often used for patients who show signs of progression despite first-line therapy [9,13,24]. PRRTs are composed of a chelator-bound radionuclide attached to an SSTR ligand [24]. When administered, the PRRT binds to the SSTR on the pNET cells to deliver β-radiation emission [13,24]. To date, their use is primarily based on data in patients with gastroenteropancreatic neuroendocrine tumors [24].

When liver metastases are present, liver-directed therapies include RFA, cryoablation, transarterial embolization, and transarterial chemoembolization [9,13]. Surgical options include metastasectomy, hepatectomy, cytoreductive surgery, and liver transplantation [13]. Systemic chemotherapy is only indicated for advanced and unresectable pNETs, with common regimens including agents such as streptozocin, cisplatin, dacarbazine, doxorubicin, and 5-fluorouracil [9,13]. The decision of which modality to select should be a multidisciplinary decision based on the type of pNET, clinical phenotype, extent of disease, anatomy, and comorbidities [13].

Aside from medical therapy, surgical resection is the only definitive treatment for Cushing syndrome from a pNET when the primary tumor and metastases are resectable [10,13]. The extent of surgical therapy depends on the extent of disease and can span from a simple enucleation to a Whipple procedure [10,13]. One study suggests that the 5-year survival rate following resection is around 90% and the recurrence rate is 12-25% [25]. When liver metastases are present, cure from surgery is possible in 10-25% of patients, the 5-year recurrence rate is 80%, and the 5-year survival rate is 85% [13].

During treatment of ectopic ACTH syndrome, cortisol levels must be closely monitored because prolonged exposure to high levels of ACTH and acute withdrawal can precipitate adrenal insufficiency [26]. This can take some time to recover, so replacement steroid therapy may need to be used when serum or urine cortisol levels fall [26].

Follow-up requires close monitoring via both physical examination and serum studies for functional pNETs. CT or MRI imaging is recommended every 6-12 months for functional pNETs for the first 3 years, then every 1-2 years for the following 10 years [25]. At present, there is no consensus on the frequency of measurements for biomarkers, but the North American Neuroendocrine Tumor Society recommends that when a patient has a functional pNET with elevation of a specific neuropeptide or hormone, measurement of the hormone in conjunction with radiological tests should be done to monitor for recurrence [9,15].

Conclusions

This rare case of an ectopic ACTH-producing pNET presenting as Cushing syndrome outlines the intricacies in both workup and multidisciplinary management, especially since a pituitary microadenoma posed as a diagnostic confounder. This required correct interpretation of a high-dose dexamethasone suppression test and further abdominal imaging to arrive at the correct diagnosis. Once an accurate diagnosis is made, treatment of pNETs involves a multimodal approach including medical

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management, with options such as ketoconazole and somatostatin analogs, as well as surgical resection. Patients with functional pNETs require very close postoperative follow-up to monitor for adrenal insufficiency. Surveillance includes physical examination, serological studies, and imaging, given the high recurrence rate. Our case described here emphasizes the critical role of early recognition, accurate localization, and tailored therapeutic strategies in managing rare presentations of ACTH-secreting tumors.

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