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Cushing's syndrome is a rare and often severe disease associated with increased mortality and major metabolic complications with cardiovascular disease as the main cause of death. Adrenal masses are most often found by radiographic studies or autopsy as incidentalomas. The prognosis of Cushing's syndrome is mainly affected by the difficulties in timely diagnosis and treatment of the disease, which remain a challenge due to its nonspecific presentation and multitude of etiologies. Herein, we present an atypical case of adrenal Cushing's syndrome unveiled by the workup of a nonfunctioning pituitary macroadenoma. A 62 year-old woman presented with new intermittent headaches and worsening vision changes for the past year. She was found to have a large sellar mass measuring 2.7 x 2.4 x 3.0 cm invading the right cavernous sinus with displacement of the optic chiasm on brain magnetic resonance imaging (MRI). In the interim to neurosurgical evaluation, lab work performed to assess pituitary function showed an elevated late night salivary cortisol at 0.200 UG/DL (0.010–0.090 UG/DL range). Low early morning ACTH and elevated late night salivary cortisol, dexamethasone suppression test and 24 hour urine cortisol were observed and confirmed with repeat studies. These findings warranted a computed tomography (CT) adrenal mass protocol which revealed a left adrenal lesion consistent with a lipid rich adenoma measuring 4.9 x 3.5 x 4.1 cm in size. Subsequent urine catecholamines and metanephrines were within normal limits. The patient was admitted for transphenoidal pituitary resection with perioperative stress dose corticosteroids, but was only able to achieve partial resection due to large tumor size. Post-operatively the patient did well on a quick corticosteroid taper down to hydrocortisone 15 mg in AM and 5 in afternoon with hope to wean in the near future. Post-operative workup showed ACTH 4.6 pg/mL (7.2 – 63.3 pg/mL) and 8 am cortisol 24.7 MCG/DL (6.2–19.4 MCG/DL) which suggests autonomous adrenal secretion of cortisol. Once the patient has recovered from her partial pituitary resection she will be referred to general surgery for adrenalectomy. This case provided a review of a classic pituitary macroadenoma workup with an interesting twist to Cushing's etiology as the cause was not from the pituitary as originally thought.

Adrenal

ADRENAL CASE REPORTS

Ectopic ACTH-Producing Pheochromocytoma as a Rare Cause for Rapid Progressing Cushing Syndrome: A Case Report

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Background: Cushing syndrome due to ectopic CRH or ACTH secretion can be rarely caused by pheochromocytoma, commonly as part of genetic conditions. **Case:** A 21 year-old male, previously healthy, with no usual medication, went to the physician assistant for hematuria. The kidney US revealed, besides lithiasis, a highly vascularized mass in the right adrenal gland with 10 cm. In his first evaluation the patient had no complaints or pheochromocitoma/hypercortisolism stigmata, other than hand tremor and slight rounding of the face. Blood pressure was 149/88 mmHg, and heart rate 86 bpm. There was no family history of endocrine disease. He rapidly developed increased appetite, insomnia, and severe myalgias, with filling of supraclavicular fossae, facial plethora, and cervical and truncal acne. Laboratory analysis showed abnormal overnight dexamethasone suppression test (57.4 µg/dL, N < 1.8), elevated ACTH 378 pg/mL (N 9.0–52.0), 24h-urinary free cortisol (UFC) (5334.0 µg/24h, N 4.3–176.0), and late-night salivar cortisol (1.44 µg/dL, N < 0.32), hypokalemia (2.8 mEq/L, N 3.8–5.0), and leukocytosis ($22.4*10^9$/L, N 4.0–11.0); DHEA-S 962 µg/dL (N 80–560), 4-androstenedione 380 ng/dL (N 70–360), 17-OH progesterone 4.5 ng/mL (N 0.59–3.44), cromogranine A 6063 ng/mL (N 0–100), and markedly elevated urinary amines (adrenaline 173 nmol/24h, N 0–109; noradrenaline 5033 nmol/24h, N 89–473; normetanephrine 334605 nmol/24h, N 480–2424; metanephrine 15998 nmol/24h, N 264–1729; dopamine 4808 nmol/24h, N 424–2612). Hypercalcemia with hypophosphatemia and supressed PTH level was also detected. 68Ga-DOTANOC PET revealed a mass of the right adrenal gland with overexpression of somatostatin receptors (likely pheochromocytoma), without evidence of other tumor lesions of neuroendocrine origin. Pituitary MRI showed normal pituitary gland. Potassium supplementation, alpha-blockade with phenoxybenzamine, and metyrapone were initiated. Due to severe back pain, a CT scan of the spine was performed detecting compressive osteoporotic fractures in the mid dorsal and low dorsal segments. The patient was submitted to right adrenalectomy. Histology revealed pheochromocytoma with 11.2*9mm, with capsular and vascular invasion, extra-adrenal extension, necrosis, and atypical mitosis, with Ki67 of 9.5% and PASS score of 16. Postoperative analysis showed ACTH 45.6 pg/mL (N 7.2-63,3), late-night salivar cortisol < 0,0544 µg/dL (N < 0,32) and free urinary cortisol 41.4 µg/24h (N 4.3–176.0). **Discussion:** Ectopic cushing syndrome caused by pheochromocytoma is a rarely described entity. In this young patient, it caused rapid clinical progression of hypercortisolism with important hydroelectrolytic disturbances and compressive vertebral fractures, requiring prompt surgical intervention for clinical remission and improvement.

Adrenal

ADRENAL CASE REPORTS

Ectopic Adrenal Tumor in a Patient With Untreated Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

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Case Presentation: A 43 year-old female was diagnosed at birth with non-salt wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency and underwent clitoral reduction surgery. She was treated with hydrocortisone and had menarche at age 7 with irregular and heavy menses. At age 15 she had a D&C with removal of "something in her ovaries." She stopped hydrocortisone at age 30 except for stress doses during illness. At age 35 she stopped oral contraceptives and thereafter has been amenorrheic. She presented with abdominal distention and constipation. On exam she had short stature, marked frontal and temporal balding, hirsutism, increased musculature and a large distended abdomen. Labs showed AM cortisol 3.1 mcg/dL (nl 10–20), ACTH 440 pg/ml (nl <46), 17-OH Progesterone 11000 ng/dL (nl <206), DHEAS 362 mcg/dl (nl <430), FSH 0.2 mIU/ml, LH 2.7 mIU/ml, testosterone 618 ng/dl (nl 10–75), and estradiol 162 pg/ml (nl post menopause <41). MRI showed a massive fibroid (30 cm), bilateral adrenal hyperplasia and a left paraaortic, retroperitoneal mass (5.9 cm). She underwent hysterectomy with removal of a 9.5 kg uterus containing degenerated fibroids, left adrenalectomy and removal of the left paraaortic mass that was initially read as oncocytic adrenal cortical neoplasm, metastatic. A similar oncocytic neoplasm was noted in the left adrenal gland and on further review with pathology the revised report read paraaortic mass, probable adrenal rest tumor.

Discussion: Excess androgens and chronically elevated ACTH levels in untreated CAH can lead to adverse effects beyond adrenal insufficiency and virilization. We present a woman with untreated classic CAH who developed a large fibroid and paraaortic adrenal cortical tumor. Fibroids have been described in CAH patients, a potential consequence of elevated androgens that are converted by aromatase in the endometrium to estrogens driving growth of fibroid tumors. Chronic ACTH can further act as a growth factor, leading to adrenal hyperplasia, adrenal tumors and ectopic adrenal rest tissue. Intra-adrenal tumors in untreated CAH are generally benign with rare cases of adrenal cortical carcinoma reported. Ectopic adrenal rest tissue in untreated CAH is most commonly reported in testes. There have been rare case reports of ectopic adrenal rest tumors in the adnexa, broad ligament, and perirenal area. Our patient presents as an unusual case of ectopic adrenal rest tumor in the paraaortic region. Based on the atypical location and incomplete history available to the pathologist, it was initially read as metastatic adrenocortical carcinoma. Upon further review given the clinical information, the diagnosis was revised to indicate a pararenal adrenal rest tumor. This case highlights the importance of glucocorticoid compliance in CAH and the necessity to provide a clinical context for the pathologist in cases of extra-adrenal tumors in untreated CAH.

Adrenal

ADRENAL CASE REPORTS

Ectopic Cushing's Syndrome and Severe Hypocalcemia Due to Medullary Thyroid Cancer Responsive to Selpercatinib

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Introduction: Cushing's syndrome (CS) due to ectopic ACTH production from medullary thyroid carcinoma (MTC) is characterized by rapid progression of disease, leading to hyperglycemia and hypokalemia. However, hypercortisolemia leading to hypocalcemia is rarely seen. Initiation of selpercatinib greatly improved hypocalcemia and ectopic CS in this case. **Clinical Case:** A 41-year-old man with a history of MTC (variant RET p.M918T) post thyroidectomy in 2018 developed progressive weight gain, lower extremity edema, weakness, new onset diabetes, severe refractory hypocalcemia and hypokalemia requiring multiple hospitalizations. On initial presentation to our institution, he was lethargic, had multiple ecchymoses, peripheral edema and proximal myopathy. Laboratory evaluation revealed Ca 5.4 mg/dL (NR 8.9 - 10.3), albumin 3 g/dL (NR 3.5 - 5.1), iPTH 1.4 pmol/L (NR 1.6 - 6.9), 25-OH vitamin D 23 pg/mL (NR 25–80) while taking elemental calcium 1500 mg every 6h, calcitriol 0.25 mcg/d and vitamin D3 1000 IU/d. Serum cortisol measured at 9:30 pm was 136 ug/dL (NR 2.5–11.9), ACTH 1,145 pg/mL (NR 7.2–63.3) and 24-h UFC 27,629 ug/d consistent with CS due to ectopic ACTH production. Calcitonin and CEA were 18,687 pg/mL (NR 0–7.5) and 3,766 ng/mL (NR 0–4.7). CT abdomen revealed numerous bilateral liver lesions and bilateral adrenal hyperplasia. In addition to high doses of oral calcium and calcitriol, he required calcium drip up to 1.5mg/kg/hr for about 1 week. He simultaneously began cabozantinib, ketoconazole and metyrapone. Hospital course was complicated by infections and recurrent scrotal bleeding, so he was switched to selpercatinib. Two days after starting selpercatinib, ketoconazole was discontinued, and metyrapone has been gradually reduced. Most recent calcitonin was 149 pg/mL, CEA 97.8 ng/mL and 24-h UFC 10 ug/d on metyrapone 250 mg twice daily. Similarly, refractory hypocalcemia greatly improved, last serum Ca was 8.3 mg/dL on elemental calcium 480 mg/d. He has made significant clinical gains and has returned home from rehab. **Clinical Lesson:** Hypocalcemia is rarely described as a complication in patients with CS. Our patient had underlying hypoparathyroidism and vitamin D deficiency; however, hypocalcemia was initially refractory to high doses of calcium and calcitriol and only improved with treatment of CS. We suspect hypercortisolemia impaired 25 to 1,25 D activation, thereby reducing calcium absorption, and likely inducing hypercalciuria. These deleterious effects of severe hypercortisolemia combined with underlying hypoparathyroidism led to severe and refractory hypocalcemia requiring repeated admissions, and only improved once his ectopic CS due to MTC was recognized and controlled. The RET kinase inhibitor, selpercatinib, induced a rapid decline in calcitonin, CEA and ACTH levels, and with metyrapone, enabled control of hypercortisolemia and its complications.

Adrenal

ADRENAL CASE REPORTS

Efficacy of Treatment With PARP Inhibitor and Immunotherapy for Aggressive Adrenocortical Carcinomawith Cushing's Syndrome Refractory to Treatment With EDP Chemotherapy and Mitotane

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