A 70-year-old female with liver cirrhosis on spironolactone and chronic bronchitis on inhaled steroids (ICS) presented for altered mental status. Laboratories showed hyponatremia 131 mmol/L (135–145 mmol/L) and hyperammonemia 113 μmol/L (11–51 μmol/L). She was successfully treated with oral lactulose for hepatic encephalopathy. However, on day 3, she developed worsening hyponatremia (126 mmol/L) and hyperkalemia 5.8 mmol/L (3.5–5.4 mmol/L). Spironolactone was discontinued, and hyperkalemia improved after medical treatment. Nonetheless, hyperkalemia recurred with worsening hyponatremia (125 mmol/L), hypoglycemia (57 mg/dL), and mild non-anion gap metabolic acidosis without other signs or symptoms of adrenal insufficiency. On day 5, her morning cortisol was 1.5 μg/dL (5–20 μg/dL), with ACTH 11 pg/mL (6–70 pg/mL). Her hyperkalemia persisted (6.3–6.8 mmol/L), and she was started on oral patiromer. Due to suspected adrenal insufficiency, she received dexamethasone 10 mg daily, and endocrinology was consulted. On day 7, an ACTH stimulation test (250 μg IV) showed a baseline ACTH <3 pg/mL, baseline cortisol 0.7 μg/dL (3–15 μg/dL), cortisol 30 minutes 9.9 μg/dL, and 60 minutes 12.2 μg/dL, consistent with incomplete response attributed to the supraphysiologic dexamethasone versus chronic ICS. On day 8, endocrinology discontinued dexamethasone and enoxaparin, and started hydrocortisone 10 mg orally in AM and 5 mg in PM. Aldosterone (measured at day 6) was 7.2 ng/dL (<= 31.0 ng/dL), renin activity 3.1 ng/mL/hr (0.5–4.0 ng/mL/hr), and aldosterone/renin ratio 2.3 (<= 25) consistent with hyporeninemic hypoaldosteronism since aldosterone and renin were inappropriately normal for the hyperkalemia. Repeat cosyntropin test on day 11 showed low ACTH (3 pg/mL), low baseline cortisol 1.1 μg/dL, cortisol 30 minutes 7.9 μg/dL, and 60 minutes 11.2 μg/dL, consistent with secondary adrenal insufficiency, ascribed to chronic ICS. Potassium level normalized seven days after spironolactone discontinuation, related to its approximate duration of action[1]. The patient was discharged with hydrocortisone 10 mg daily, and spironolactone was permanently discontinued.

Spironolactone use can result in type 4 RTA due to aldosterone resistance and mimic mineralocorticoid deficits characteristic of primary adrenal insufficiency.

1. O'Connell JE, Colledge NR. Type IV renal tubular acidosis and spironolactone therapy in the elderly. *Postgrad Med J*. 1993;69(817):887–889.

Adrenal

ADRENAL CASE REPORTS

Unlikely Coexistence of Sporadic Pheochromocytoma and Bilateral Macronodular Adrenal Hyperplasia: A Challenge to Manage

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Background: The incidence of bilateral macronodular adrenal hyperplasia (BMAH) is unknown, but growing in an era of increased utilization of imaging. Coexistence of BMAH and pheochromocytoma has not previously been reported.

Clinical Case: A 63-year man presented with enlarging left chest-wall mass found to have a poorly differentiated sarcoma. Staging PET/CT identified a hypermetabolic 2.0 cm left adrenal nodule with SVU of 16.6 concerning for metastasis. Hormonal evaluation included dexamethasone suppression test with 7AM serum cortisol of 24.7 ug/dL (<1.8 ug/dL) without dexamethasone level, serum ACTH <5.0 pg/mL (7.2–63 pg/mL), plasma metanephrine of <0.20 nmol/L (0–0.49 nmol/L), and plasma normetanephrine of 0.76 nmol/L (0.00–0.89 nmol/L). Biopsy of this left adrenal nodule was consistent with pheochromocytoma. By history, he lacked any classical symptoms of pheochromocytoma. Repeat testing demonstrated only slight elevations in normetanephrine (1.3 nmol/L and 1.2 nmol/L); he remains asymptomatic at follow-up 4 months later. However, history and exam revealed central obesity, thin skin, type 2 diabetes mellitus on insulin, and hypertension controlled on three agents concerning for Cushing's. Repeat evaluation showed AM cortisol of 17.9 ug/dL (<1.8 mcg/dL) with dexamethasone level of 917 ng/dL (180–550 ng/dL), ACTH of 6.4 pg/mL with concordant cortisol of 23.1 ug/dL, and 24 hour urine collection with 0.98 L volume, creatinine of 0.58 g/24h (1–2 g/24hr), and urinary free cortisol of 67 ug/24h (3.5–45) altogether suggesting ACTH-independent hypercortisolism. On review of CT abdomen, he has bilateral adrenal nodules measuring >1cm with bilateral gland enlargement consistent with BMAH. Resection of his left adrenal gland was not pursued due to cormorbidities as well as biochemically-silent nature of his pheochromocytoma. To manage his hypercortisolism, he was recently initiated on osilodrostat after completing radiation therapy for his chest-wall sarcoma.

Conclusion: This is the first case demonstrating clinical, biochemical, and imaging results consistent with bilateral macronodular adrenal hyperplasia and hypercortisolism also found to have a clinically and biochemically silent, biopsy proven pheochromocytoma. This is also a unique use of osilodrostat to manage BMAH.

Adrenal

ADRENAL CASE REPORTS

Unusual Presentation of Cyclic Cushing's Syndrome

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Introduction: About 20–40% of patients with Cushing's syndrome present with cyclic Cushing's Syndrome characterized by episodes of cortisol excess interspersed with periods of normal cortisol secretion. A high degree of suspicion is needed to identify patients with cyclical hypercortisolism. Fluctuations in cortisol levels can make this a diagnostic challenge. Rarely, hypocortisolemia and frank adrenal insufficiency can occur.

Case Report: A 77-year-old female with history of Cushing's syndrome and transsphenoidal surgery with no adenoma identified on pathology presented with fatigue and concern for recurrence with ACTH of 358 pg/mL (6–50 pg/mL) and morning serum cortisol of 41.4 mcg/dL. Brain MRI showed a possible 4 mm pituitary adenoma. However, when she was transferred to our hospital, there was no evidence of hypercortisolism with cortisol of 9.5 mcg/dL, ACTH of 33pg/mL, 24 hr urine free

cortisol (UFC) of 4.4ug/d (<45ug/d) and she was discharged home after neurosurgery recommended no surgical intervention. A week later, the patient returned to the hospital with nausea and weakness, and found to have cortisol of 4.4mcg/dL, ACTH of 12 pg/mL and UFC of 2.8 ug/d requiring short course of hydrocortisone for adrenal insufficiency. One year later, she presented with hip fracture, worsening weakness, plethora, and facial swelling. UFC was 1,338.3mcg/24 hr(4.0–50.0 mcg/24 hr), AM serum cortisol 58.8mcg/dL and ACTH 304.7 pg/mL. In addition to severe osteoporosis with hip fracture, she had hypertension and impaired fasting glucose. She was treated with Ketoconazole 200mg daily which was titrated until AM cortisol levels decreased from 58.8 mcg/dL to 20 mcg/dL. Patient was discharged on Ketoconazole with plan to complete a Dotatate scan to evaluate for ectopic ACTH production which resulted negative. Shortly thereafter, she returned with hypotension, nausea, and fatigue. Repeat cortisol level was 2.3 mcg/dL with ACTH of 27.6 pg/ml. Ketoconazole was discontinued and patient was started on hydrocortisone for adrenal insufficiency. Hydrocortisone was gradually tapered off. Pituitary MRI and IPSS are planned for further evaluation.
Discussion: Cyclic Cushing's syndrome is diagnosed with three peaks and two troughs of cortisol production. Diagnosis and treatment are challenging since the cycles of hypercortisolism can occur sporadically and rapid fluctuations in cortisol makes it difficult to localize a source. Cortisol fluctuations can affect quality of life and result in complications such as diabetes, hypertension, and osteoporosis. Prompt identification of the source of the Cyclic Cushing's syndrome is vital to pursue definitive therapy. However, in 9% of cases, there is no identifiable source. In such cases, medical therapy is warranted.

Adrenal

ADRENAL CASE REPORTS

Variations in the Initial Presentation of a Rare Congenital Adrenal Hyperplasia: Steroidogenic Acute Regulatory Deficiency

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Background: Steroidogenic Acute Regulatory (StAR) deficiency is a rare form of congenital adrenal hyperplasia characterized by dysregulated cholesterol transport mediated by StAR enzyme across mitochondrial membranes. Adrenal dysfunction is due to the two-hit hypothesis: 1) defective StAR protein and 2) cholesterol accumulation in the adrenals and gonads. With variable cellular damage, adrenal crisis can occur early or late. **Clinical cases:** We present two cases of StAR deficiency with contrasting presentations. Case 1: A 9-day old ex full term female from a nonconsanguineous union presented to a rural hospital with hypothermia, lethargy, and poor feeding. She had hypoglycemia 41 mg/dL (60–105), hyponatremia 120 mEq/L (135–145), hyperkalemia 7.7 mEq/L (3.5–5.5) and cortisol < 0.4 ug/dL (4.5–23). Baby was started on hydrocortisone (HCT) 100 mg/m^2 and one-time fludrocortisone (FCT). She decompensated requiring chest compressions, intubation and pressors. She was transferred to our institution. Newborn screen was normal; she had typical female external genitalia. US demonstrated a uterus; ovaries and adrenals were not identified. Upon extubation and clinical improvement, her HCT was weaned to physiologic doses. She became hyponatremic requiring FCT and salt supplements. Post-HCT wean, ACTH level was 304 pg/mL (7–63) with aldosterone < 4.0 ng/dL (6.5–86). Karyotype was 46,XX. Genetic analysis revealed a novel heterozygous likely pathogenic variant in the *STAR* gene, (*STAR* c.65-12_68del variant) without defect in the other *STAR* gene. Case 2: A 9-month-old ex full-term female of Iraqi descent from a nonconsanguineous union presented with fatigue, poor oral intake and weight loss from 50%-ile to 3%-ile. She had hyponatremia 122 mEq/L, hyperkalemia 8.0 mEq/L, but was normoglycemic. She was normotensive; EKG was normal. Parents noted progressive hyperpigmentation including her gums, palmar and plantar creases. She had typical external female genitalia with a hypoplastic clitoris (2 mm x 2 mm). ACTH stimulation test showed low cortisol (0.5 ug/dL) at 60 minutes. She was treated with HCT 100 mg/m2 for 5 days, then tapered to maintenance dosing, with FCT and salt supplements. Her ACTH level returned > 5000 pg/ml. Aldosterone, 17-OH-Progesterone, 17-OH-Pregnenolone, 11-Deoxycortisol and androstenedione were undetectable. Pelvic US did not identify uterus or ovaries. Pelvic MRI identified bilateral inguinal testes with enlarged adrenal glands. Karyotype was 46, XY. We suspected StAR deficiency with sex-reversal. Genetic analysis revealed a known homozygous mutation in *STAR* (c.545G>A). **Conclusion:** StAR deficiency is clinically indistinguishable from P450scc deficiency and genetic testing is needed. Both entities can present with early or delayed adrenal crisis. While classic for StAR deficiency, adrenal enlargement is inconsistent. Karyotype is vital to identify sex reversal.

Adrenal

THERAPEUTIC TRIALS AND PROGNOSTIC MARKERS FOR ADRENAL DISEASES

Biochemical Tumor Marker Status and Its Role in Treatment Response in Patients Who Received High-Specific-Activity I-131 MIBG in Advanced Pheochromocytoma and Paraganglioma (PPGL): Results From a Pivotal Phase 2 Clinical Trial

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Background: High-specific-activity iodine-131 meta-iodobenzylguanidine (HSA I-131 MIBG; AZEDRA®) has