representing <6% of these cases. No guidelines exist on the management of these tumors.

Clinical case: A 41-year-old woman presented to the ED with a 6-month history of newly-diagnosed T2DM and difficult-to-control hypertension. Three weeks prior to admission she developed fatigue, dyspnea on exertion, and generalized weakness particularly severe in the lower extremities (LE) limiting her ability to ambulate. She denied headaches, palpitations and diaphoresis. Initial vital signs included HR 111 beats/min and BP 217/112 mmHg. On physical exam she had classic findings of CS with severe LE weakness. Laboratory testing was consistent with ACTH-dependent CS (ACTH 463 pg/mL [0-45], cortisol 70.8 mcg/dL [3-23], potassium 2.7 mMol/L [3.1-5.1]). She failed both the low dose (1 mg) and high dose (8 mg) dexamethasone suppression tests. MRI of the pituitary gland ruled out a pituitary lesion. IPSS was not deemed necessary by Neurosurgery. CT abdomen showed a 4.2 cm right adrenal lesion and bilateral adrenal hyperplasia. This prompted workup for pheochromocytoma that revealed elevated plasma metanephrines (4.1 nMol/L, [<0.5]) and 24hr urine metanephrines (5329 mcg/day, [182-739]). A diagnosis of APP was entertained. Doxazosin 1 mg BID was added to her other antihypertensives with improvement in blood pressure. Ketoconazole 200 mg TID was started as a bridge for surgery. Patient underwent right unilateral adrenalectomy one month after initial presentation. ACTH and cortisol levels before surgery were 534 pg/mL and 87 mcg/dL, respectively, suggesting that ketoconazole was not effective. Both ACTH and cortisol levels decreased to 26 pg/mL and 14.4 mcg/dL, respectively, immediately after surgery. There was prompt subjective symptomatic improvement, including mild recovery of LE strength. Her blood pressure normalized and only spironolactone was continued. She was started on a prednisone taper. Pathology revealed a 4.2 pheochromocytoma and diffuse adrenocortical hyperplasia. Tumor cells stained positive for ACTH on immunohistochemistry. On follow up visit 2 months after surgery patient was feeling well and ambulating without difficulty. Labs were remarkable for normal plasma fractionated metanephrines, and A1c 5.1% on metformin alone (down from 4 medications on initial presentation).

Conclusion: Diagnosis and management of APP can be challenging. Alpha-blockers should be started promptly. Definitive treatment with unilateral adrenalectomy is curative and has been recommended as the preferred approach.[1] Ketoconazole may be used as bridge therapy for surgery, though some studies suggest its efficacy might be lower in ectopic CS.[2] Response to other pharmacologic agents is largely unknown.

References:
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Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Establishing the Link Between Genetic Variations of Estrogen Receptor 2 and Unexplained Infertility

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Background: Unexplained or idiopathic infertility comprises approximately 30% of couples who present with infertility. This has led to investigations seeking to determine the cause(s) of this important diagnosis of exclusion. Estrogen's role in reproduction has been well- established. Estrogens bind to two hormone receptors (namely estrogen receptor-alpha and estrogen receptor-beta), which are distributed differentially throughout the body. Specifically, the estrogen receptor-beta, coded by the Estrogen Receptor 2 (*ESR2*) gene, is highly expressed in granulosa cells and growing follicles. The one female patient reported with an *ESR2* mutation presented with hypergonadotropic hypogonadism. However, subfertility with inefficient ovulation and resistance to exogenous ovulatory stimulation is seen in an *ESR2* knockout mouse model. We therefore hypothesized that less severe *ESR2* variants could lead to a normal female phenotype and pubertal development but could be a cause subfertility.

Methods: DNA samples from 200 women with unexplained infertility were obtained from the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial, which investigated optimal ovulation induction medications for unexplained infertility. These samples were subjected to targeted next-generation sequencing (NGS) for the *ESR2* gene. Likely pathogenic variants that occurred with a minor allele frequency of < 0.01 in the gnomAD database and a Combined Annotation Dependent Depletion (CADD) score of > 20 were selected for confirmation by Sanger sequencing.

Results: From the 200 patient samples, five heterozygous missense variants and one heterozygous in-frame deletion identified by targeted NGS were confirmed by Sanger sequencing. Further studies will need to be performed *in vitro* to confirm the likely pathogenicity of these variants.

Conclusion: These studies raise the possibility that If these variants in *ESR2* that impair estrogen signaling, they could be a potential newly recognized etiology of unexplained infertility in women with unexplained infertility.

Conclusion: These studies raise the possibility that variants in *ESR2* that impair estrogen signaling could be a potential newly recognized etiology of unexplained infertility in women.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Artifactual Hypoglycemia in a Patient with Prolonged Hospital Stay for Neuroleptic Malignant Syndrome

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MON-699

Background: Hypoglycemia is rare in patients without diabetes. A low capillary glucose concentration is not sufficient