

of the serum calcium towards tolerable values, the tumor was removed by open en bloc adrenalectomy. Histologic evaluation confirmed an ACC (TNM pT4 pN1 (2/3), L1, V1, high grade) despite missing immunohistochemically expression of classical adrenal markers (diagnosis of exclusion). Supplemental quantitative RT-PCR studies support the diagnosis of ACC by detecting significant SF-1 and CYP11B2 expression in the tumor cells. Further analyses provided evidence that the mRNA expression of PTH, but not PTHrP, was moderately increased in the ACC sample compared to NCI H295R cells. Upon tumor resection, serum calcium levels swiftly normalized indicating the tumor as the sole source of PTH secretion. Despite initiation of adjuvant mitotane- and salvage chemo-therapy, the patient died 3 months later upon of a massive tumor relapse with a recurrence of severe hypercalcemia. **Conclusion:** This case demonstrates paraneoplastic hypercalcemia in a PTH producing ACC. PTH may induce hypercalcemia, impair adrenal steroid synthesis and act as an autocrine growth factor in ACC, as described in few individual cases for PTHrp producing ACC [1]. This suggests a poor prognosis for this rare entity.

1. Rizk-Rabin, M., et al., Differential Expression of Parathyroid Hormone-Related Protein in Adrenocortical Tumors: Autocrine/Paracrine Effects on the Growth and Signaling Pathways in H295R Cells. 2008.

Thyroid

HPT-AXIS AND THYROID HORMONE ACTION

TSH Is a Negative Modulator of Hippo Transcriptional Effectors

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Hippo signaling pathway regulation by hormonal signals acting through G-coupled receptors has been widely described. Modulation of processes such as tissue growth or differentiation by this pathway critically relies on the location and levels of its major effectors: the cofactors YAP/TAZ and the family TEAD of transcription factors. Despite this well-defined regulatory mechanism, little is known about the Hippo pathway in the thyroid gland. Thyrotropin (TSH), main factor for thyroid follicular cells differentiation, plays its role by interacting with its G-protein-coupled receptor (TSHR). High serum TSH levels are associated with hypothyroidism, characterized by a change in thyroid follicle morphology and inflammation of the thyroid gland. This led us to study if TSH could modulate the Hippo pathway. Rat thyroid follicular cells (PCC13) were treated with TSH and forskolin, an adenylyl cyclase activator. By immunofluorescence and western blot, levels and subcellular location of the Hippo Pathway components were assessed in different conditions. An increase of the Hippo kinase MST1/2 and LATS1/2 was observed after TSH and forskolin treatments, corresponding to a downregulation of the transcriptional mediators of the pathway TAZ, YAP and Tead1. Especially remarkable is the translocation of YAP/TAZ from the nucleus, which involves a decrease in their activity. Next, we validated the results in an *in vivo* model generating hypothyroidism in 3-month-old male C57BL/6J by adding MMI

(2-Mercapto-1-Methylimidazole) and perchlorate (KClO₄) to their drinking water. After 2 weeks of treatment, we euthanized the animals, validated higher TSH serum levels and performed analysis of the Hippo components in the thyroid by immunohistochemistry. A reduction in the levels of the Hippo effectors TAZ, YAP and Tead1 was found in the thyroid slices from hypothyroid mice, confirming the *in vitro* results. In addition, evaluation of a human thyroid tissue microarray, including Hashimoto disease samples, led to a validation of the previously described TSH role. Hereby, we report a crosstalk by which TSH is increasing the kinase axis of the Hippo pathway thus decreasing the activity of its main transcriptional effectors in the nuclei. Future research of the role of these transcriptional effectors will be carry out to discern if their decrease could be associated with the morphology changes linked to hypothyroidism.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Euglycemic Diabetic Ketoacidosis on Initiation of Ertugliflozin in a Patient With Type 2 Diabetes Mellitus Precipitated by a Ketogenic Diet

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Background: Diabetic ketoacidosis (DKA) is defined by metabolic acidosis, ketosis and hyperglycemia. It is considered to be a consequence of significant insulin deficiency and/or insulin resistance and is usually precipitated by the presence of hyperglucagonemia or other counterregulatory hormones. In patients on oral sodium-glucose cotransporter 2 (SGLT2) inhibitors, decreased carbohydrate availability through renal glucose excretion can cause serum glucose levels to be lower than what is normally seen (< 200 mg/dL) in DKA cases, masking the diagnosis. This phenomenon is termed euglycemic DKA (EuDKA). Existing evidence suggests that EuDKA in the setting of SGLT2 inhibitor use is rare and occurs mostly in patients with type I diabetes mellitus (T1D) and seldom in type 2 diabetes mellitus (T2D). Most published reports of EuDKA in patients with T2D describe patients on SGLT2 inhibitors with clear inciting events such as decreased insulin doses, surgery, or severe acute illness. To our knowledge, none have reported EuDKA precipitated by ertugliflozin. This is also the first report of EuDKA of a patient in the United States with T2D initiating SGLT-2 inhibitor use while on a low carbohydrate diet. **Clinical Case:** A 53-year-old female with a history of poorly controlled T2D was admitted to the hospital with EuDKA within seven days of starting ertugliflozin and alogliptin. Patient admitted to strict adherence to a low-carbohydrate diet for one week prior to admission. On admission, the patient was afebrile. Initial labs showed blood glucose 104 mg/dL, serum bicarbonate 8 mmol/L, anion gap 22, pH 7.100, beta-hydroxybutyrate 66.94 ng/mL (0.20-2.81), and a hemoglobin A1c of 11.2%. Urinalysis revealed glucosuria ≥500 mg/dL, ketonuria 80 mg/dL, hyaline cast 20/lpf, no nitrites or leukocyte esterase, WBC 1/hpf. Flu PCR negative. WBC count was 17.4 x10³/uL initially, though all CBC cell lines decreased with