replenish steroidogenic cells of the zG and the inner cortex over time (1). Both the fate of progenitor cells and aldosterone production by steroidogenic cells in the zG are regulated by Wnt signaling (2,3), but the cell-specific effects of individual Wnt ligands in the adrenal are not fully understood. To further characterize Wnt signaling components crucial for progenitor cell maintenance and zG identity, we analyzed mouse adrenals using single molecule *in situ* hybridization (smISH), which revealed the previously unknown expression of *Wnt2b* exclusively in the adrenal capsule. *Wnt2b* is co-expressed with the Wnt signaling potentiator *Rspo3*, the loss of which causes zG depletion and reduced adrenal size in mice (4). Therefore, we hypothesized that capsular WNT2B activates Wnt signaling in the underlying cortex to maintain the undifferentiated state of progenitor cells. To define the role of WNT2B in these processes, we generated *Wnt2b* conditional knockout (cKO) mice by crossing a capsule-specific *Gli1-CreERT2* driver (5) and a floxed *Wnt2b* allele (6). We administered tamoxifen to 6-week-old male mice and assessed the effects of *Wnt2b* loss 4 weeks later. Gli1-CreERT2 activation significantly decreased *Wnt2b* expression ($P<0.001$) and resulted in a lower adrenal to body weight ratio in *Wnt2b* cKOs compared to controls ($P<0.05$). Adrenocortical proliferation (Ki67) was significantly decreased in *Wnt2b* cKO mice ($P<0.0001$), suggesting that WNT2B may mediate progenitor cell self-renewal. To characterize the effect of WNT2B loss on Wnt signaling, we assessed activation of the primary Wnt effector β-catenin. High β-catenin activity in the zG observed in wild-type mice was disrupted in *Wnt2b* cKO mice, together with markedly reduced expression of adrenocortical Wnt target genes *Axin2* and *Wnt4*. In addition, *Wnt2b* loss resulted in downregulation of steroidogenic genes *Cyp11b2* ($P=0.0139$) and *Hsd3b6* ($P=0.0679$). Together, these data suggest that capsule-derived WNT2B activates cortical Wnt signaling to maintain the identity of both undifferentiated progenitor cells and differentiated steroidogenic cells of the zG, which has important implications for adrenal homeostasis and disease, including both primary adrenal failure and neoplasia.

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Adrenal

ADRENAL CASE REPORTS III

Acute Paraneoplastic Cushing's Syndrome in a Patient With Small Cell Lung Cancer and Co-Incidental Adrenal Adenoma: A Case Report

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MON-LB039

Background: Paraneoplastic Cushing's syndrome is a rare cause of hypercortisolism associated with high morbidity, especially in patients with small cell lung cancer. Therefore, early diagnosis and treatment are critical.

Clinical Case: Herein we present the case of a 58-year-old man who was referred to the endocrinology department, because of refractory hypokalemia (potassium 2.4 mmol/l; RI: 3.4 - 4.5 mmol/l) despite high potassium supplements and spironolactone therapy. History was remarkable for a metabolic syndrome with newly aggravated hypertension and a 60-pack-year smoking history. The patient reported a 20 kg weight gain in 6 weeks and proximal muscle weakness. On examination, he was overweight (BMI 44.8 kg/m²) with bilateral pitting edema. Other features of hypercortisolism such as striae rubrae, facial plethora or ecchymoses, respectively, were not apparent. Initial biochemical tests showed severe hypokalemia and metabolic alkalosis. Night-time salivary cortisol (205 nmol/l; RI: < 2.5 nmol/l), 24-hour urinary free cortisol (> 4357 nmol/24h; RI: 99 - 378 nmol/24h) and serum ACTH (158 ng/l; RI: < 61 ng/l) were markedly elevated. While the MRI of the head demonstrated no pituitary pathology, the CT of thorax and abdomen revealed a pulmonary mass as well as an incidental right adrenal mass. Bronchoscopic biopsy of the pulmonary mass confirmed the suspected diagnosis of ACTH-producing small cell lung cancer. The dignity of the right adrenal mass remained unclear, since the radiologic features *per se* could not differentiate between adrenal adenoma and metastasis. Chemotherapy with cisplatin/etoposide and inhibition of steroidogenesis with ketoconazole were initiated, which largely controlled the hypercortisolism. Imaging studies after completion of two cycles of chemotherapy showed a tumor response with regression of the pulmonary mass. The right adrenal mass remained stationary under chemotherapy. Thus, an adrenal metastasis could be excluded as potential cause of the adrenal mass, suggesting an incidental adrenal adenoma as the most likely diagnosis.

Conclusion: Paraneoplastic Cushing's syndrome requires high clinical suspicion for early diagnosis, since many of the classical clinical features of hypercortisolism may still be absent, even if the underlying cancer is already advanced. In patients suspected to have Cushing's syndrome a three-step diagnostic approach is recommended: (1) biochemical confirmation of hypercortisolism, (2) differentiation between ACTH-dependant and -independant hypercortisolism and (3) identification of its source. This approach helps avoiding misdiagnosis in patients who have both an ACTH-producing cancer and an adrenal adenoma [1].

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Thyroid

NO LONGER A PAIN IN THE NECK — RECENT INSIGHT INTO THYROID GROWTH, DEVELOPMENT, AND PATHOLOGY

Increased BMI Is Associated With Anti PD-1/PD-L1-Induced Thyroid Immune-Related Adverse Events

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OR28-07

Background: Immune checkpoint inhibitors have revolutionized cancer therapy, however, are associated with immune related adverse events (irAEs). Obesity is a pro-inflammatory metabolic state that may play a role in the development of irAEs. **Hypothesis:** We hypothesized that likelihood of developing thyroid irAEs following anti-PD-1/L1 therapy increases with increasing body mass index (BMI). **Methods:** We retrospectively analyzed data of 187 cancer patients who initiated anti-PD-1/L1 at our institution between 01/2014-12/2018, had normal thyroid function tests at baseline and had baseline BMI data available. **Results:** Overall, 97 (52.2%) patients were with low-normal BMI (<25 kg/m^2), 52 (28.0%) overweight (≥25-30 kg/m^2) and 37 (19.9%) obese (≥30 kg/m^2). Thyroid dysfunction (hyper or hypo, overt or subclinical) developed in 72/187 (38.7%) patients, of whom 29/97 (29.9%) had low-normal BMI, 22/52 (42.3%) were overweight and 21/37 (56.8%) obese (p=0.14). With every 1 kg/m^2 increase in BMI, the likelihood of thyroid dysfunction increased by 8.8% (p=0.004). Overt hyperthyroidism occurred in 32/186 (9.1%) of the patients - in 4.1% of patients with low-normal BMI, 11.5% of overweight patients and 18.9% of obese (p=0.006). Overt hypothyroidism occurred in 32/186 (17.2%) of the patients and was not significantly associated with BMI. Hyperthyroidism followed by overt hypothyroidism, consistent with thyroiditis, occurred in 13/186 (7.0%) of patients and was significantly associated with increasing BMI category (p=0.03). **Conclusions:** Increased BMI was associated with increased thyroid irAEs in patients treated with PD-1/L1 inhibitors. Further exploration of the interaction between obesity and immunotherapy may provide insight into the role of inflammation in mediating immune response.

Adrenal

ADRENAL CASE REPORTS III

Uncommon Findings in Beckwith-Wiedemann Syndrome

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MON-LB036

Introduction: Beckwith-Wiedemann syndrome (BWS) is characterized by variable phenotypes that might include overgrowth, macroglossia, abdominal wall defects, neonatal hypoglycemia, hemihypertrophy and predisposition to embryonal tumours.

Some features are more specific, including adrenal cytomegaly. BWS increases risk for several tumors, including adrenocortical tumor (ACT). Some protocols recommend screening with adrenal ultrasonography and serum DHEAS every 4–6 months.

Case report: A 1-month-old male, preterm (34 weeks 4 days), large for gestational age (weight 3670g), presented with macrosomia, macroglossia, umbilical hernia and auricular pits, with clinical diagnosis of BWS. In newborn screening 17 alpha hydroxyprogesterone (17OHP): 70,15 ng/mL (<15ng/mL) and 66,32 ng/mL in second sample. Presented basal cortisol 11.4 mcg/L (6,70 a 22,60 µg/dL), normal electrolytes, dehydroepiandrosterone sulphate (DHEAS) > 1000 mcg/dL (30,0 - 250,0 mcg/dL), testosterone 637 ng/dL (60-400 ng/dL), leading to ACT suspicion. No suppression of cortisol (2,8 mcg/dL) after dexamethasone 10 mcg/kg. Urinary metanephrines were normal, plasmatic normetanephrine 554 pg/mL (<196 pg/mL) and plasmatic norepinephrine 2094 pg/mL (< 420 pg/mL). Abdominal CT showed increased adrenal glands, with normal contrast uptake. MRI and PET/CT DOTA-68Ga did not identify tumors. Eight months later: 17OHP 0,88 ng/mL (0,8-5ng/mL), DHEAS 37 mcg/dL (<30,0 mcg/dL), testosterone 13 ng/mL (< 30 ng/dL), normal urinary metanephrines and plasmatic catecholamines.

Conclusion: In this case congenital adrenal hyperplasia was ruled out and ACT was suspected. Imaging did not identify tumors and biochemical findings (hypercortisolism and high androgens levels) had progressive improvement. Bilateral adrenal hyperplasia may be present in BWS as a result of fetal adrenal gland delay maturation. Permanent adrenal cortex cytomegaly may be responsible for hypercortisolism. Transient cortex persistence can lead to androgens elevation and produces large amounts of DHEA, that could explain DHEAS elevation similar to that in ACT. Bilateral adrenal hyperplasia is described as a feature of BWS, but, to our knowledge, there is no similar case in literature with these biochemical findings.

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Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Radioligand Theranostics of Endocrine-Related Cancers; A New, Revolutionary Approach

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SUN-LB26

Radioligand Theranostics of Endocrine-Related Cancers: A New, Revolutionary Approach

The successful clinical development of octreotide targeting somatostatin receptors (SSRs) revolutionized treatment of Neuro Endocrine Tumors (NETs)and pituitary adenomas. Recently, clinical applications of peptide bioconjugates including octreotide have taken a giant leap forward into a new diagnostic and therapeutic arena of additional endocrine-related cancers including prostate,