

mutation. Three months after, her acne and frontal hair loss were better, and a trial of spironolactone 50 mg daily, was prescribed. For her sister and mother was suggested to consult endocrinology, due to possible same disease.

**Conclusion:** this case highlights the importance of recognizing NCCAH as a cause of hyperandrogenism. Molecular genetic analysis should be offered with genetic counseling to patients, since they can carry a severe allele which can affect their progeny. Clinicians should be aware of the importance of family history when diagnosing NCCAH on their patients; for detection, treatment and genetic counseling of NCCAH on family members as well, as found in this case.

## Tumor Biology

### ENDOCRINE NEOPLASIA CASE REPORTS I

#### *Rare Case of Ectopic Cushing Syndrome Caused by ACTH Secreting Thymic Neuroendocrine Tumor in a Patient with Multiple Endocrine Neoplasia Type 1.*

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#### SUN-938

##### Introduction

Cushing syndrome (CS) represents an uncommon manifestation of MEN1 and can be caused by both ACTH dependent or independent etiologies. Among them, ectopic ACTH secretion from a Thymic neuroendocrine tumor (TNET) in MEN1 is rare, with very few cases reported so far in literature. We report a case of Ectopic Cushing syndrome (ECS) in a MEN1 patient (pt) with multiple tumors, secondary to ACTH-secreting TNET.

##### Case description:

A 44 year old male presented to our institution for nausea, vomiting, dizziness. He had initial workup which revealed multiple tumors (papillary thyroid cancer, thymic mass, parathyroid adenomas, bilateral adrenal nodules, macroprolactinoma, peripancreatic nodules). Given concern for MEN 1, genetic testing was performed which was confirmative. Hormonal workup at this time for adrenal nodules was negative including low dose dexamethasone suppression test(DST). The immobile thymic mass was found to be poorly differentiated NET on biopsy with Ki-67 >50% with vascular invasion and adhesions to lung/chest wall on VATS, not amenable to surgery. The pt declined chemotherapy and radiotherapy due to poor social support. Six months later, he presented with complaints of shortness of breath, proximal muscle weakness, anasarca. Evaluation revealed AM cortisol >60 ug/dL(range 6.7-22), high-dose DST Cortisol >60 ug/dL, 24hr urine free cortisol: 8511mcg (range 4-50) and ACTH level: 278pg/mL(range 6-50) confirming ACTH-dependent CS. Special stains from the previous TNET biopsy demonstrated positive staining for ACTH confirming ectopic ACTH secretion. Ketoconazole and chemotherapy with Etoposide and Carboplatin was started, however he clinically deteriorated and expired a few weeks after diagnosed of ECS.

##### Discussion:

TNET in MEN 1 is rare, with a prevalence of 3-8%. TNET are unusual neoplasms that account for 2% to 7% of all

mediastinal tumors. TNET in MEN1 rarely secrete functional hormones with very few reported Ectopic ACTH secretion. MEN1 associated ECS from TNET is an aggressive disease with local invasion of adjacent mediastinal structures or metastasis being common, resulting in poor prognosis as demonstrated in few case reports including our case. Radical surgery of involved adjacent structures and adjuvant local RT can provide local disease control.

##### Conclusion:

Our pt is a rare case of ECS from TNET in MEN1 with poor prognosis. A special feature of this case is that the patient had initial negative evaluation for hypercortisolemia, however 6 months later he presented with signs and symptoms of severe hypercortisolism, with evaluation confirming transformation into ACTH producing TNET. This conversion is very rarely found in literature and adds to the unique presentation of the case.

## Diabetes Mellitus and Glucose Metabolism

### METABOLIC INTERACTIONS IN DIABETES

#### *Metabolic and Functional Regulation of T Cells by Insulin and Insulin like Growth Factor 1*

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#### SUN-649

Obesity leads to altered immunity characterized by increased risk of autoimmunity, poor response to infection, and impaired vaccine response. T cells play an important role in this obesity-associated immune response; however, the mechanisms by which T cells are altered in obesity remain unknown. Our goal is to identify nutritionally regulated hormones and cytokines that link whole body nutrition and immunity, and to understand the mechanisms by which such factors can alter T cell response in obesity. To that end, we have identified the hormones insulin and insulin-like growth factor-1 (IGF-1) as potential links between nutritional status and T cell metabolism and function. Insulin is secreted from pancreatic beta cells in response to increasing blood glucose levels, and circulating insulin levels are elevated in obesity due to insulin resistance in metabolic tissues. IGF-1 levels are influenced by protein intake and nutrition status, and free (bioactive) levels of IGF-1 are elevated in obesity. To study the role of insulin and IGF-1 on T cell function and metabolism, we treated activated CD4 T cells with physiologic levels of insulin or IGF-1 in vitro for 24 hours. Treatment of CD4 T cells with insulin or IGF-1 increased glucose uptake, glycolytic metabolism, and mitochondrial metabolism while altering inflammatory cytokine production. In particular, both insulin and IGF-1 decreased IFN- $\gamma$  production, whereas IGF-1 specifically increased IL-17 production from both bulk activated CD4 T cells and T cells skewed toward a T helper 17 (Th17) phenotype. Using a T cell-specific insulin receptor (IR) conditional knockout mouse, we found that loss of IR signaling decreased glucose uptake and mitochondrial metabolism and increased IFN- $\gamma$  production by activated T cells. Moreover, IR appears to be required for both insulin and IGF-1 effects on T cells.

Lastly, we investigated the CD4 T cell subset-specific expression of both IR and IGF-1 receptor (IGF-1R). We found that each CD4 T cell subset had its own unique expression of both IR and IGF-1R; however Th17 cells had a striking increase in IGF-1R expression compared to the other T cell subsets, indicating a specific role for IGF-1 in promoting inflammation. These findings underscore the ability of the nutritionally-regulated hormones insulin and IGF-1 to modulate CD4 T cell metabolism and function and thereby alter T cell immunity, which has direct clinical relevance in both normal physiology and in obesity.

## Tumor Biology

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

#### *Estrogen Induces Granulocytic Myeloid Derived Suppressor Cell Production to Potentially Modulate Lymphangiomyomatosis (LAM) Tumor Progression*

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#### SUN-134

Affecting almost exclusively women, lymphangiomyomatosis (LAM) is a rare lung disease characterized by estrogen-sensitive metastatic smooth muscle cell-like adenomas that grow slowly, resulting in cystic lung change and loss of pulmonary function. LAM tumors are caused by mutations in tuberous sclerosis complex 1 or 2 genes (*TSC1* or *TSC2*). Mutations in *TSC1* or *TSC2* genes results in deficient inhibitory regulation of the mammalian target of rapamycin complex 1 (mTORC1), which in turn leads to increased mTORC1 activity and cell proliferation. There is no consensus amongst LAM researchers regarding the origin of these estrogen receptor-positive smooth muscle like LAM cells; however, we previously reported inactivation of *TSC2* in the mouse uterus results in notable LAM features in the setting of primary myometrial tumors. Approximately 50% of the *TSC2*-null mice had metastatic myometrial tumors present in the lung, suggesting that LAM tumor cells might in fact originate from the uterus, thus explaining the female sexual dimorphism, the estrogen sensitivity, and the metastatic nature of the LAM tumors.

Interestingly, flow cytometry revealed large numbers of granulocytic myeloid derived suppressors cells (G-MDSCs) in the blood and myometrial tumors of uterine-specific *Tsc2* null mice. MDSCs are known to accumulate in the setting of chronic inflammation caused by trauma, infection, and various cancers. This granulocytic subtype not only has the capacity to suppress anti-tumor immune cells of the tumor microenvironment, but also directly promotes tumor cell malignant neoplasticity. We found that *Tsc2*-null myometrial tumors required MDSCs for normal progression, as MDSC depletion or inhibition of MDSC recruitment reduced tumor growth. We have showed that these tumors expressed estrogen receptors and were exquisitely sensitive to estrogen, while other studies demonstrate that G-MDSCs are also positively influenced by estradiol. Therefore, we hypothesized that, in addition to direct effects of estrogen

on tumor cells, estrogen also stimulates tumor growth by promoting MDSC production in the bone marrow. We have developed a technique to stimulate MDSC production from mouse bone marrow. Using this strategy, we found that estradiol is indeed a potent promotor of G-MDSC production. These effects occurred in both male and female bone marrow. Employing both pharmacologic agents and bone marrow from ER $\alpha$ ; knockout mice, we showed that ER $\alpha$ ; is necessary for promoting a G-MDSC fate for immature myeloid cells and precursors. Thus, estradiol may have dual effects in LAM, both directly promoting tumor growth and indirectly upregulating MDSC production, which in turn promotes tumor growth. We propose that these estrogen effects on MDSC production are not limited to LAM and may be important regulators of tumor growth in many tissues.

## Diabetes Mellitus and Glucose Metabolism

### CLINICAL AND TRANSLATIONAL GLUCOSE METABOLISM AND DIABETES

#### *Retrospective Analysis of the Contribution of Cannabis Usage to Diabetic Ketoacidosis at an Urban Teaching Hospital*

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#### MON-615

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes mellitus. It is responsible for greater than 100,000 hospital admissions per year in the US (1). There are few studies regarding the relationship between drug usage and acute diabetic complications (2). Since 2001, cannabis usage among US adults have more than doubled, as state legal restrictions have eased and attitudes towards cannabis have become more permissive. Cannabis is the most commonly used illicit drug in the US (3). Some studies suggested cannabis usage was associated with improvement in insulin sensitivity and pancreatic beta cell function. Other research demonstrated cannabis usage may contribute to diabetes-related hospitalizations.

A retrospective analysis was performed at an urban teaching hospital to examine the relationship between cannabis usage and risk for DKA upon presentation. From March 2017 to February 2019, all non-pregnant patients aged 18 years and older, and who met criteria for DKA admission upon medical records review, were included in the study. Demographics, vitals, biochemistry, and toxicology were evaluated. Overall, 188 admissions for DKA were identified in a total of 130 patients, and 43% (81/188) were readmissions by 23 patients.

Illicit substance usage was addressed by history in 72% (135/188) of all admissions, among which 24% (33/135) reported cannabis usage. 36% (67/188) of all admissions, 73% (24/33) of the self-reported cannabis usage group, and 46% (37/81) of the readmissions, underwent general toxicology screening that did not include detection for cannabis. 11% (20/188) of all admissions, 24% (8/33) of the self-reported cannabis usage group, and 16% (13/81) of the readmissions, completed toxicology screening specifically for cannabis.