SUN-305

Diagnosis of endogenous Cushing's syndrome entails corticotropic autonomy, lack of circadian rhythm and/or hypercortisolism, evaluated through 24h urinary free cortisol (UFC). Hair cortisol measurement (HCM) has been described as an alternative marker of cortisol exposure over the preceding three months.

OBJECTIVES To evaluate HCM in Cushing's disease (CD). To analyze the correlation between HCM and UFC. To compare HCM values in CD vs controls.

PATIENTS AND METHODS 3 cm hair from posterior vertex in CD and in controls age- and gender-matched between May 2017 and May 2019. Controls were low level stressed individuals (Holmes-Rahe's scale) without adrenal disease. Normal reference interval of HCM was defined (40-128 pg/mg hair). Measurement: Siemens Immulite 2000 (Gwynedd, UK) automated chemoluminiscent immunoassay (CLIA)

UFC values within the 3 months previous to hair collection were considered. Controlled CD defined as UFC ≤1 upper normal limit (UNL) with or without treatment, remission as UFC ≤1 without pituitary lesion. Results are presented as median (m) and range. Kruskal-Wallis ANOVA used for median difference evaluation and Kappa index for concordance determination. Chi2 test for comparison of recategorized UFC and HCM. Statistical analysis performed with SPSS 23.0

RESULTS

23 CD patients recruited, median age 42 ± 11 years; 91% (n=21) female; 10 samples collected at diagnosis and 13 during follow-up. Control group composed of 50 individuals

45% (n=10) had controlled CD (mUFC 0.42 UNL, range 0.1-0.9) and a mHCM of 134.5 pg/mg (62-334) and 55% (n=12) did not have control (mUFC 2.2, 1.1-6) and a mHCM of 150.5 (75-459). After recategorization of UFC (> o ≤ 1 UNL) and HCM (> o ≤ 128 pg/mg), determinations were associated (Chi2, p= 0.18), however, the concordance was acceptable (Kappa index = 0.276).

After dividing CD patients according to HCM, 35% (n=8) had normal HCM: mHCM 113.5 (62-126) and mUFC 0.45 (0.1-4.4). Among them, 63% (n=5) had controlled CD (mHCM 110, 62-121; mUFC 0.39, 0.1-0.85); 25% (n=2) had active CD (mUFC 2.7, 1.1-4.4; mHCM 121, 75-126). 65% had high HCM (n=15): mHCM 167 (132-459) and mUFC 1.36 (0.1-6). Most of them had active CD (n=11, 73%): mHCM 160 (132-459) and mUFC 2.2 (1.1-6). Four patients with elevated HCM (m 248, 148-334) had normal UFC (m 0.61, 0.12-0.92): 2 were in remission, 1 had normal postsurgical UFC with active disease in the follow-up and 1 had normal UFC under medical treatment.

Controls (n=50) had mHCM 62.5 (40-126), significantly different from CD.

CONCLUSIONS

We evaluated HCM in CD, proposing this method as an additional diagnostic test for hypercortisolism. The acceptable concordance between UFC and HCM is possibly due to the different duration of the evaluated periods.

The difference in the HCM values observed between controlled or active CD patients and controls permits the consideration of the method as an alternative in the diagnosis and/or follow-up of CD.

Thyroid

BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID I

Vitamin D Levels and Risk of Thyroid Immune Related Adverse Events in Patients on Immune Checkpoint Inhibitors

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SAT-411

Immune checkpoint inhibitors (ICI), such as monoclonal antibodies to cytotoxic T lymphocyte associated protein 4 (CTLA-4), programmed cell death 1 (PD-1) and PD ligand 1 (PD-L1) are recognized as effective cancer-directed therapies. Yet, ICI-induced activation of the immune system results in immune-related adverse events (irAEs) affecting many organs, including the thyroid. Separately, Vitamin D (Vit D) deficiency has been associated with increased risk of autoimmune thyroid disease. We hypothesized that patients who were Vit D deficient at the time of initiating ICI therapy would be more likely to develop thyroid irAEs. We retrospectively collected data for 411 patients who received ICIs at our institution between January 2011 and April 2017. We then identified 91 of these patients who had 25-OH Vit D levels obtained; 2 were excluded from analysis due to previous thyroidectomy. We recorded demographics, cancer type, Vit D level closest to the start date of ICI therapy, and thyroid irAEs. Patients were categorized as Vit D deficient (<20ng/mL), insufficient (20-29.9ng/mL) or sufficient (≥30ng/mL). We compared patient demographic and clinical characteristics between the VitD categories. Proportions were compared using Fisher's Exact Test. Of the 89 patients, 48.3% were female and 51.7% were male. Mean age was 67.2 (SD±10.6) years with 57% white, 8% black, 10% hispanic, 7% Asian, and 18% other / unknown. 20% of patients had non-small cell lung cancer, 15% melanoma, 13% hepatocellular carcinoma, 12% multiple myeloma (MM), 8% renal cell carcinoma (RCC), 7% head and neck squamous cell carcinoma, 7% urothelial carcinoma and 18% other cancer types. 21.3% were Vit D deficient, 40.4% were insufficient, and 38.2% were sufficient. Patients with Vit D deficiency and insufficiency were younger (age 64.1± 11.7, 65.9±9.5 years, respectively) than the Vit D sufficiency group (70.1±10.5years, p=0.046). No significant differences between males and females were observed between Vit D categories. Across cancer types, the highest prevalence of Vit D deficiency was in RCC (42.9%) and MM (36.4%). Hispanic and Asian patients had the highest prevalence of Vit D deficiency (44.4% and 33.3%, respectively). 11 patients (12.4%) developed a thyroid irAE. Thyroid irAEs occurred in 5.3% with Vit D deficiency, 8.1% with Vit D insufficiency, and 20% with Vit D sufficiency, but the association was not statistically significant (p=0.2). In

contrast to our hypothesis, Vit D deficiency was not associated with a higher rate of thyroid irAEs. In fact our data suggest that patients who are vitamin D sufficient at the time of starting ICI therapy may be at greater risk of developing thyroid irAEs. Our study is limited by small numbers and the retrospective nature of the study. Prospective studies should be performed to determine the significance of Vit D levels on ICI related thyroid disease.

Adrenal

ADRENAL CASE REPORTS II

Delayed Diagnosis of Cushings Syndrome: Hiding in Plain Sight!

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SUN-157

Background: Endogenous Cushing's syndrome (CS) is rare, with an incidence of 0.7-2.4/million people/year.[1] It should be considered in individuals with diabetes (DM), hypertension (HTN), osteoporosis or electrolyte abnormalities.[2] We present a patient with DM2 and persistent hypokalemia for 10 years found to have ACTH-independent Cushing's disease as the cause of metabolic syndrome. **Case:** 62 y.o. M admitted with abdominal pain, a history of DM2 (2012) on Metformin 500 mg BID, HTN (2010) and on ramipril 10 mg qd, with chronic lymphedema on furosemide 20 mg qd. He reported 3-inch height loss. On exam, had facial plethora, moon facies, supraclavicular fullness, thick violaceous abdominal striae and kyphosis. Past history was significant for abdominal/leg cellulitis, muscle weakness, difficult to heal wounds, easy bruising and recurrent hospitalizations for hypokalemia, despite being on KCl up to 80 mEq/d for 10 years. Labs showed AM cortisol at 22.6 ug/dL, ACTH <5 pg/mL, 24-hour urine free cortisol of 523 ug/d (normal < 60 ug/d). AM cortisol after 1 mg overnight dexamethasone suppression was 36.8 g/dL, ACTH <5 pg/mL. CT abdomen showed right adrenal nodule, 4.0 x 3.5 cm with density of 22 HU. MRI showed lipid-poor adenoma measuring 3.9 x 3.5 cm, raising concern for adrenocortical malignancy. Patient underwent right adrenalectomy. Pathology was consistent with benign adenoma showing no nuclear pleomorphism, lipid rich cells containing eosnophillic cytoplasm. Mib-1 stain <1% cells and positive inhibin. He was maintained on steroids post op due to concern about adrenal insufficiency. Hypokalemia, DM and lymphedema resolved completely 4 months post op with weight loss of ~30 pounds. HbA1c improved to 5.1%, metformin was stopped and he was maintained on Carvedilol 6.125 mg BID for HTN. He was diagnosed with osteoporosis with T score -4.0 at mean femoral neck, -2.9 for mean total hip with non-diagnostic spine. He had multi-level chronic compression fractures of the mid-thoracic spine. **Conclusion:** Delayed diagnosis of CS, as occurred in our patient, can result in detrimental consequences such as life threatening electrolyte abnormalities, cardiovascular events, fractures and premature death.[1] Identifying CS can be challenging as clinical presentation is variable. [2,3] Early recognition, diagnosis and control of CS is crucial to decrease morbidity and mortality. Our patient demonstrated rapid resolution of DM, hypokalemia and lymphedema after surgery; however, prolonged exposure to endogenous cortisol resulted in compression fractures and osteoporosis requiring follow up treatment. **References:** 1. Ille I et al, The Multifarious Cushings. Acta Endocrinol.2019 15(2):261-269 2. Reimondo G et al, Lab differentiation of Cushings syndrome. Clin Chim Acta. 2008;388(1-2):5-14 3. Fan L et al, Association of hypokalemia with cortisol and ACTH levels in Cushings disease. Ann N Y Acad Sci. 2019

Steroid Hormones and Receptors

STEROID BIOLOGY AND ACTION

A Prospective Non-surgical Treatment for Inguinal Hernias

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SAT-747

Background: Inguinal hernias are a widespread public health issue and typically diagnosed in one-fourth of all men. Despite hernia repair being the most commonly performed surgery in the US, the mechanisms causing this disease are currently unknown. We previously developed a mouse model that expresses the human aromatase gene (*Arom*^{hum}) wherein all male mice develop inguinal hernias. We further showed that high production of estradiol by aromatase in the lower abdominal muscle (LAM) via binding to estrogen receptor caused increased fibroblast proliferation and muscle atrophy which leads to inguinal hernia formation (1).

Hypothesis: Disruption of estrogen signaling via ablation of estrogen production using an aromatase inhibitor or inhibition of estrogen receptor by an estradiol antagonist can prevent or reverse the formation of inguinal hernias.

Results: We previously demonstrated that aromatase inhibitor, letrozole, completely prevented the formation of inguinal hernias in *Arom*^{hum} mice (1). Here we show that ER-dependent estradiol antagonist fulvestrant can also prevent LAM tissue fibrosis, muscle atrophy and hernia formation in *Arom*^{hum} mice (n=4, p=0.0007). WT littermates did not show hernia formation with or without fulvestrant treatment (n=4). Furthermore, we demonstrate that aromatase inhibitor letrozole can reverse mild to moderate size of hernia (150-160 mm^2), while placebo-treated mice had progressively enlarged hernias (n=7, p=0.04). We subsequently show a reduction in muscle fibrosis and a restoration of myocyte size in *Arom*^{hum} mice with letrozole treatment.

Conclusion: Estrogen produced as a result of aromatase expression in estrogen-sensitive LAM tissue stimulates the proliferation of estrogen receptor-expressing fibroblasts, fibrosis, muscle atrophy, and hernia formation. Ablation of estrogen production or its signaling not only completely prevents this phenotype but also reverses mild to moderate-sized hernias. Our findings pave the pathway for developing the first potential preventive and therapeutic pharmacological approach for combating recurrent inguinal hernias in elderly men through modulation of estrogen signaling in abdominal muscle tissue.