

detachable) and less stiff (i.e. more pliable) based on atomic force microscopy analysis of individual cells. Notably, AKR1C3, an aldo-keto reductase, which is elevated frequently in advanced prostate cancer, showed marked upregulation in SULT2B-deficient cells. AKR1C3 regulates androgen receptor (AR) signaling by promoting androgen biosynthesis and functioning as an AR-selective coactivator. While levels of AR and DHT did not change, AR activity was elevated, since PSA and FKBP5 mRNA induction by DHT-activated AR was several fold higher in SULT2B-silenced cells. The DHT-metabolizing AKR1C2 aldo-keto reductase was also upregulated, which likely accounts for a steady-state androgen level despite elevated AKR1C3 expression. Phosphorylation of ERK decreased in AKR1C3-silenced cells, signifying a causal link between AKR1C3 upregulation and ERK1/2 activation. SULT2B was undetectable immunohistochemically in tissue microarrays of clinical CRPC metastases, while SULT2B-negative samples showed AKR1C3-positive immunostaining. Primary prostate cancer exhibited variable, Gleason score independent SULT2B levels -- varying from strong positive to significantly reduced or undetectable. The reciprocal expression pattern for SULT2B and AKR1C3 in clinical CRPC suggests that AKR1C3 upregulation, ERK1/2 activation and increased aggressive traits of SULT2B-ablated cells, observed *in vitro* in cell models, may be clinically significant. Pathways regulating the inhibitory SULT2B-AKR1C3 axis may inform new avenue(s) for delaying disease progression in SULT2B-deficient prostate cancer. Funding Support: 1I01BX000280, VA (BC); W81XWH-14-1-0606, DOD (BC); IK6 BX004207, VA (BC); P50 CA97186, NIH & W81XWH-12-1-0208, DOD (EAM)

## Thyroid

### THYROID DISORDERS CASE REPORTS II

#### *Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis: Diagnosis or Distraction?*

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#### SAT-465

In 1966 a case of episodic encephalopathy with anti-thyroid antibody (ATAb) positive Hashimoto's thyroiditis was first reported. Controversy persists regarding Hashimoto's encephalopathy, now known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and any relationship with ATAb. There is no literature supporting an etiologic role of ATAb in SREAT. Nor has there been correlation shown between ATAb titer and severity of thyroid dysfunction or SREAT(1).

A 56 yo female was admitted to a community hospital three times with visual hallucinations and slurred speech. Brain MRI, LP and standard tests including C3/C4, folate, B12, ANA and ANCA were unrevealing. Thyroglobulin antibodies (TgAb) and anti-thyroid peroxidase antibodies (TPOAb) were positive. Diagnosed with SREAT with relief of symptoms on high dose IV corticosteroids. Discharged on

oral prednisone. Seven months later she began experiencing progressive proximal weakness of all extremities associated with exertional dyspnea, fatigue and weight gain. EMG studies indicated steroid-induced myopathy of the proximal extremities. After prednisone tapering, she was admitted to our institution with acute confusion, blurred vision, fever, tachycardia, tachypnea and hypoxemia.

Examination showed Cushingoid features. Labs showed hyperglycemia, ANA (+), TPOAb (+), TgAb (+), low FreeT4, low T3, normal TSH and elevated IgG in the CSF. Brain MRI showed meningeal enhancement of parieto-occipital lobes and left tentorium. Empiric antibiotics started to cover infectious meningoencephalitis. Endocrinology consulted for iatrogenic Cushing's syndrome with hyperglycemia, abnormal thyroid function tests (TFTs) with positive ATAb and evaluation for SREAT. We recommended tapering steroids and evaluation for infectious, autoimmune or paraneoplastic causes of encephalopathy, before presuming SREAT. Rheumatological and infectious work-up was negative. CT chest showed nodular densities and CT abdomen showed hepatic, splenic and right inguinal region masses. Biopsy of inguinal mass showed Diffuse Large B-cell Lymphoma confirmed on bone marrow biopsy. CSF flow cytometry was unrevealing, likely due to prior steroids. Leptomeningeal enhancement likely reflected leptomeningeal metastases. Treated with systemic R-CHOP, high dose MTX, intrathecal MTX, cytarabine and corticosteroid tapering. Complete remission was achieved with normalization of TFTs, resolution of her Cushingoid and encephalopathic features.

This case illustrates SREAT as a diagnosis of exclusion. ATAbs may be positive in non-thyroid autoimmune disorders, other neurological conditions and 10-20% of the general population (2). B cell lymphoma with leptomeningeal metastasis caused encephalopathic features which improved with corticosteroids. Ascribing a diagnosis of SREAT led to delayed cancer diagnosis and treatment.

## Cardiovascular Endocrinology

### PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

#### *Vitamin E Sequestration by Liver Fat in Vitro and in Women with Hepato-Steatosis*

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### SUN-555

**BACKGROUND:** The global obesity epidemic has sobering consequences to human health. Especially concerning is obesity-associated hepato-steatosis (HS), a common cause of chronic liver disease in the Americas and Western Europe that precedes non-alcoholic steatohepatitis (NASH). Maintenance of normal body weight is the only current means to prevent HS and NASH. We hypothesized that excess liver fat in obesity-associated HS could act as a pathophysiologic chemical depot for fat-soluble vitamins and alter normal physiology. Because clinical trials with Vitamin E ( $\alpha$ -T) have shown that NASH partially responds to this supplement, we selected  $\alpha$ -T as a model vitamin to test the sequestration hypothesis.

**INTERVENTIONS:** Under an IND and IRB-approved protocol, two deuterium-labeled  $\alpha$ -tocopherols ( $d_3$ - $\alpha$ -T and  $d_6$ - $\alpha$ -T) were administered orally and intravenously, respectively, to 10 healthy women and 6 women with HS. Serial blood samples obtained over 72 h were analyzed by LC-MS/MS. In parallel, we performed studies in hepatocytes in cell culture and mouse model.

**RESULTS:** In healthy women who received oral  $d_3$ - and intravenous  $d_6$ - $\alpha$ -T, 85% of the initial plasma peak  $d_6$ - $\alpha$ -T disappeared within 20 minute and reappeared in the plasma peaking between 6-8 h. Compared to healthy subjects, subjects with HS had similar  $d_6$ - $\alpha$ -T entry rates into liver, but reduced release rates into plasma ( $p < 0.001$ ). Similarly, pharmacokinetics parameters (AUC and Maximum Concentration [ $C_{max}$ ]), were reduced (AUC<sub>0-8h</sub>,  $p < 0.01$ ;  $C_{max}$ ,  $p < 0.02$ ) in HS subjects, indicating reduced hepatic  $d_6$ - $\alpha$ -T output. Consistently, livers of mice fed with a high fat diet (42% fat) had more vitamin E compared to controls diet (5% fat), with both diets having the same  $\alpha$ -T content

**CONCLUSION:** These findings suggest the unique role of the liver in vitamin E physiology which is dysregulated by excess liver fat (measured by magnetic resonance spectroscopy). Considered together, the findings imply that obesity-associated HS may produce unrecognized hepatic  $\alpha$ -T sequestration, which might subsequently drive liver disease. The data here raise the intriguing possibility that timely  $\alpha$ -T supplementation might attenuate progression of HS to NASH, perhaps by correcting an unrecognized fat-induced, localized, hepatic vitamin E deficiency prior to onset of inflammation, hepatitis, and fibrosis. Additionally, our findings raise the possibility that HS may similarly alter hepatic physiology of other fat-soluble vitamins.

## Thyroid

### THYROID CANCER CASE REPORTS I

#### *Metastatic Renal Cell Carcinoma (RCC) to the Thyroid: Case Report and Clinical Lesson*

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### SUN-479

**Background:** Metastatic neoplasms to the thyroid gland are rare and have been observed more in autopsy series than in clinical series.

**Case:** A 71-year old woman presented for thyroid nodule evaluation which was incidentally noted on CT/PET scan. She was diagnosed with renal cell carcinoma (RCC) stage IV (6.4 cm, left nephrectomy) 4 months prior. She had right hemi-thyroidectomy 30 years prior for a benign nodule. She was clinically and biochemically euthyroid with dysphagia and hoarseness in her voice. Thyroid u/s revealed multiple nodules in the left lobe with a dominant 3.6 x 2.9 x 3.6 cm solid, heterogeneous nodule with grade 3 hypervascularity. History positive for 1 cm right renal mass and multiple pulmonary nodules increasing in size thought to be consistent with metastases. The FNA of the dominant nodule was indeterminate, Bethesda III (AUS), GSC suspicious (Affirma, 50% ROM) with negative malignancy classifiers. Patient underwent completion thyroidectomy, and surgical path was consistent multifocal clear cell renal cell carcinoma (CRCC) with the largest focus of 3 cm based on clear cell features and strong positivity for stains: CK OSCAR, RCC, PAX-8 & CD-10. Patient is currently on Pazopanib post thyroid surgery for 18 months, and is stable with no further increase in the size of lung nodules or right renal mass and negative serial PET scans.

**Clinical lesson:** CRCC represents 3-4% of all adult malignancies and 85% of all primary renal tumors. In clinical series, CRCC is the most frequent source of thyroid metastases and represents 12-34% of all secondary thyroid tumors. About 17% of patients with CRCC have metastatic disease at diagnosis. Metastases can be synchronous or metachronous to the primary tumor. Latency from nephrectomy to diagnosis of thyroid mets varies from 2 months-21.9 years. Metastases can be solitary (more common), multiple or diffuse. Radiological findings typically reveal hypoechoic and vascularized mass on ultrasound and cold on thyroid scan. Metastases to thyroid can pose diagnostic problem and be a source of confusion in cytology interpretation. Metastatic CRCC can simulate morphologically primary thyroid neoplasm such as Hurthle cell neoplasm or thyroid carcinomas with clear cell changes. Metastatic carcinoma within the thyroid gland is negative for thyroglobulin, TTF-1, calcitonin unlike primary thyroid cancer. CRCC is usually positive for periodic acid-Schiff and Oil red O, vimentin, and CD10. The mean survival in patients with CRCC who had thyroidectomy alone or with adjuvant treatment was 3 years.

**Conclusion:** Thyroid metastases should be considered in patients with thyroid nodules and positive history of RCC. The preoperative distinction between primary and secondary tumors is difficult. Immunohistochemistry is a useful method for the evaluation of patients with suspected thyroid nodules.

## Tumor Biology

### TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

#### *Secretin Stimulation Test in a Patient Receiving Proton PUMP Inhibitor Therapy- to Do or Not to Do?*

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### SAT-121

Introduction:

Complications of gastrinoma cause increase in mortality in patients with MEN syndrome. There are concerns that