

showed persistent PTH-dependent hypercalcemia (with albumin-corrected serum calcium of 10.4-10.8 mg/dl, and PTH 64-78 pg/ml), initially raising suspicion for primary hyperparathyroidism. Subsequent testing showed a low 24-hour urine calcium (82 mg/day) despite adequate daily calcium intake, robust 25-hydroxy vitamin D levels (47 ng/ml), and normal renal function. Calcium/creatinine clearance ratio was low at 0.0064 and FHH was suspected. CaSR gene sequencing revealed two heterozygous abnormalities: (1) a likely pathogenic mutation in the start codon of the CaSR (c.3G>A (p.M1?)) that has not been previously reported (p.M1? indicates that it is not known whether the mutation leads to no CaSR being produced from that allele or if an abnormal protein is produced using an alternate methionine start codon) and (2) a low-prevalence activation mutation variant of the CaSR (p.R990G), which is associated with hypercalciuria and increased risk of kidney stones but generally does not cause hypocalcemia. Genetic testing was unable to determine if these two mutations were on the same (cis) or opposite (trans) alleles. If they are on opposite alleles, the phenotype represents the heterozygous loss-of-function CaSR abnormality with compensation by an activating mutation in the opposite allele. If they are on the same allele, the activating variant is either not expressed at all due to nontranslation or is located on an abnormal/shortened protein. CaSR sequencing of the patient's daughter was normal. In the absence of recombination occurring between the two loci, this strongly suggests the two were on the same allele in this case. **Discussion:** Thus far, > 100 mutations in the CaSR gene causing FHH have been described; but to our knowledge, this case is the first report of a start codon mutation causing FHH. This happened to be identified in the setting of a low-prevalence hypercalciuric variant. Familial testing strongly suggested the two mutations were on the same allele. The activating mutation, therefore, was likely functionally silenced in this case.

## Thyroid

### THYROID DISORDERS CASE REPORTS II

#### *Conversion of Hashimoto's Thyroiditis to Grave's Disease: A Case Report*

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#### SAT-497

Conversion of Hashimoto's Thyroiditis to Grave's Disease: A case report

**Introduction:** Hashimoto's thyroiditis and Grave's disease are common causes for autoimmune thyroid disease. Conversion from Grave's disease to hypothyroidism have been previously reported in literature. But development of Grave's disease after a long standing hypothyroidism rarely occurs. **Case report:** a 22 -year-old Saudi pregnant female patient, was diagnosed with subclinical hypothyroidism with positive anti -thyroid peroxidase antibodies (Anti-TPO) in 2009. She was started on thyroxin and eventually became euthyroid with normal TSH levels till 2016. During subsequent follow-ups, patient was increasingly complaining of palpitations, weight loss and fine tremors.

Thyroid function revealed increasingly suppressed TSH levels and over-replacement was suspected. Thyroxin dose was then gradually reduced and finally stopped for few months. Yet her symptoms persisted. Repeated thyroid function showed suppressed TSH level and elevated T4, T3 levels in keeping with overt hyperthyroidism. Thyroid scan further confirmed the diagnosis with diffuse thyroid uptake suggestive of Grave's disease. Patient was started on medical treatment initially, then successfully treated with radioactive ablation. **Conclusion:** Although it rarely occurs, possibility of conversion from hypothyroidism to hyperthyroidism should always be kept in mind while treating hypothyroid patients with persistent clinical or biochemical evidence of hyperthyroidism despite dose reduction. **References:** [1] McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: Potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. *Thyroid*. 2013;23(1):14-24. [2] Ohye H, Nishihara E, Sasaki I, et al. Four cases of Graves' disease which developed after painful Hashimoto's thyroiditis. *Intern Med*. 2006;45(6):385-9.

## Tumor Biology

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

#### *Loss of DHEA-Targeting SULT2b1b Sulfotransferase Exacerbates Aggressive Traits of Prostate Cancer*

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#### SAT-114

The prostate-expressed sulfotransferase SULT2B1b (SULT2B) regulates intracrine androgen homeostasis by mediating 3β-sulfation of DHEA, thus reducing the precursor pool in the androgen biosynthesis pathway. We explored how loss of SULT2B might influence prostate cancer progression. Results show that SULT2B ablation in castration-resistant prostate cancer (CRPC) cells, generated by stable RNA interference or gene knockout, led to robust activation of the ERK1/2 Map kinase survival signal and induction of epithelial to mesenchymal transition (EMT). EMT activation was concluded on the basis of increased levels of vimentin (a mesenchymal protein) and the EMT-activating transcription factors SNAI1 (Snail) and TWIST1, shown by Western blotting, mass spectrometry and single-cell mass cytometry. Loss of SULT2B was associated with enhanced motility and invasive activity of CRPC cells *in vitro* and their growth escalation *in vivo* as xenografts. Higher invasion and metastasis potential of SULT2B-ablated CRPC cells was further indicated by results that these cells are less adhesive (i.e. easily

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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