

to also have HPT with Parathyroid Adenoma (PA) and Vitamin D Deficiency.

A 64-year-old female presented to the emergency room for social needs. She had not received medical care for the past 10 years and had known history of SC, previously treated with prednisone and methotrexate. She also noted a long-standing history of elevated calcium (Ca) up to 11 mg/dL. She was fasting for the past 1 month for spiritual reasons and was not taking any medications or supplements. Initial labs were significant for Ca of 13.2 mg/dL, Albumin 4.4 g/dL, ionized Ca 1.43 mmol/L. Creatinine was 1.1. EKG revealed T-wave inversions in V1, 2, 3. She received IV fluids and Ca improved to 11 mg/dL. HC was attributed to known history of SC. However further evaluation revealed parathyroid hormone (PTH) level high at 156 pg/mL, 25-OH Vit D level low at 8.5 ng/mL with normal 1,25 hydroxy Vit D levels at 46 pg/mL. Parathyroid sestamibi scan revealed a left parathyroid adenoma. Surgery was deferred because patient was asymptomatic and did not meet criteria for parathyroidectomy. On discharge, Ca levels remained stable and she was started on Ergocalciferol 50,000 units weekly.

HC can be either parathyroid mediated, non-parathyroid mediated, or due to medications. In primary HPT, the elevated PTH levels cause increased bone resorption through activated osteoclasts and increased intestinal Ca absorption. Malignancies involving solid tumors and leukemias can lead to HC through osteolysis and osteoclasts or PTH-related peptide. Thiazide diuretics increase renal Ca absorption that lead to mild HC which can be reversed when the medication is discontinued. Other endocrine disorders that can lead to HC include thyrotoxicosis-induced bone resorption, adrenal insufficiency and pheochromocytoma.

Management of hypercalcemia depends upon the level of Ca. Mild HC (Ca < 12mg/dL) is usually asymptomatic and improves with hydration. Asymptomatic or mildly symptomatic patients with chronic moderate HC (Ca 12-14 mg/dL) may not require immediate treatment. Severe HC (Ca >14mg/dL) is treated with IV hydration with normal saline (NS), calcitonin and zoledronic acid. Administration of calcitonin and NS results in substantial reduction in Ca within 12-48 hours.

Although, HC was initially attributed to SC, primary HPT and low 25-OH Vit D levels also contributed to HC in this patient. Thus, it is important to evaluate patients with known HC from sarcoid for other etiologies.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION

I

Segesterone Acetate (SA) Serum Levels with a Statistical Model of Continued Use of the SA/Ethinyl Estradiol (EE) Contraceptive Vaginal System

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The novel, ring-shaped, contraceptive vaginal system (CVS; Annovera™), contains 103 mg of SA and 17.4 mg of EE, and delivers a mean dose of SA 0.15/EE 0.013 mg/day. The CVS was designed to last thirteen cycles in a 21 day-in/7 day-out regimen. Objectives of these analyses were to determine the amount of SA/EE remaining in the CVS after 13 cycles of use and to estimate the SA level in serum after 1 year of continuous use.

Residual SA/EE levels from CVS used by women (n=18) for 13 cycles of 21/7 regimen in a phase 3 clinical trial were further analyzed in vitro. Hypothetical SA level in serum after 1 year of continuous use was estimated using data from 39 women who participated in a 13-cycle pharmacokinetic study of the 21/7 CVS regimen. The serum data were used to construct a statistical model for the change in serum SA concentrations from cycle 1 to cycle 13. The data from each individual subject was modeled to estimate the serum SA level based on days of use. Each subject's model was then used to estimate the serum SA level after 364 days of continuous CVS use. The average of all 364-day values from valid models was then calculated.

After 13 cycles of a 21/7 regimen, the amount of SA/EE remaining in the CVS was 61.7 mg/14.0 mg (60%/80% of the original SA/EE load), which established the release of 0.15 mg SA and 0.013 mg EE per day for a total of 273 days. The model predicted that the mean serum SA level after 364 days of continuous use was 71 pmol/L with a lower limit of the 90% CI of 52 pmol/L.

A high percentage of SA/EE remained in the CVS after 13 cycles of use. Serum SA levels predicted by the model following 1 year of continuous use were similar to those previously observed (mean 73 pmol/L) at 1 year in a SA silicone implant trial in which there were no reported pregnancies at 1 year (Sivin et al, *Contraception*. 2004;69:137-144). No pregnancy or PK data with continuous use of the CVS is available at this time. Further study on the continuous use of the CVS is warranted.

Adipose Tissue, Appetite, and Obesity

NEURAL MECHANISMS OF OBESITY

The Role of the Focal Adhesion Kinase Family in Leptin Receptor Signaling

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Overweight and obesity are global concerns affecting nearly one third of the world population. These conditions are characterized by increased adiposity and are accompanied by a proportional increase in circulating leptin, an anorexigenic adipokine. Leptin is responsible for signaling peripheral energy status to the central nervous system to modulate food intake and energy expenditure. As such, neurons within the hypothalamus expressing the long isoform of leptin receptor (LepRb), a type I cytokine receptor, are primarily responsible for mediating the effects of leptin, which signal predominantly through

the JAK2-STAT3 transduction mechanism. STAT3 is a latent transcription factor activated upon phosphorylation, which triggers its homodimerization and nuclear translocation. Evidence, however, for JAK2-independent, STAT3-dependent leptin receptor signaling mechanisms exist. FAK (focal adhesion kinase, Ptk2) and Pyk2 (protein tyrosine kinase 2b, Ptk2b) are a subset of nonreceptor protein tyrosine kinases and comprise the focal adhesion kinase family. FAK and Pyk2 are implicated in the regulation of cytokine receptor signaling. Furthermore, Pyk2 knockout mice have an obesity prone phenotype. Here, we studied the role of the focal adhesion kinases in leptin receptor signaling using genetic and pharmacological approaches. We found that overexpression of Pyk2 or FAK increased STAT3 phosphorylation (activation). Overexpression of a FAK or Pyk2 construct with impaired kinase activity, however, attenuated STAT3 phosphorylation, suggesting the increase in STAT3 phosphorylation is largely dependent upon kinase activity of FAK/Pyk2. Treatment of cells with a small molecule dual inhibitor of FAK and Pyk2 (PF431396) attenuated leptin-induced STAT3 phosphorylation in a mouse hypothalamic cell line. Importantly, this effect is independent of JAK2, as PF treatment of two independent JAK2-deficient cell lines exhibited similar attenuation of leptin-induced STAT3 phosphorylation. To assess the physiological relevance of FAK/Pyk2 in leptin receptor signaling *in vivo*, we administered PF compound to the lateral ventricle of 24-hour fasted lean wild-type mice followed by peripheral leptin administration. Intracerebroventricular (ICV) administration of PF suppressed the anorectic effect of leptin as evidenced by impaired inhibition of food intake upon refeeding. Accordingly, analysis of total hypothalamic lysates from these mice showed ICV PF impaired leptin-induced STAT3 phosphorylation. Taken together, these data suggest that Pyk2 and/or FAK play a role in leptin signal transduction.

Thyroid

THYROID CANCER CASE REPORTS II

Lower Extremity Leiomyosarcoma Metastatic to a Benign Thyroid Nodule

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Background: Metastases to the thyroid gland from non-thyroidal malignancies have been reported in 1.4-3% of patients undergoing thyroid surgery for malignant thyroid tumors, but only 4% of these are due to sarcomas¹. Metastases in a pre-existing thyroid nodule are even more rare. We present a patient with a lower extremity leiomyosarcoma that metastasized to a pre-existing benign thyroid nodule.

Clinical Case: A 70-year-old woman was referred to the Thyroid Nodule Clinic for a 5 cm thyroid nodule replacing most of the right thyroid lobe. Twenty years earlier the patient had a left thyroid lobectomy for a benign nodule. One year before presentation, she was diagnosed with a high grade lower extremity leiomyosarcoma with lung metastases and started on treatment. A large right thyroid nodule pressing on the trachea was incidentally found

on an initial chest CT performed for sarcoma staging. On PET-CT, the nodule was not FDG-avid. On ultrasound, the thyroid nodule was solid and heterogeneous, iso- to hyperechoic with smooth margins, inspissated colloid and grade 3 vascularity. Fine needle aspiration (FNA) of the nodule showed benign cytology (Bethesda II). The patient did not have local compressive symptoms and decided not to undergo surgical removal of the nodule.

The thyroid nodule was initially stable on periodic follow-up CT scans and thyroid ultrasounds. However, a thyroid ultrasound performed 2.5 years later showed a change in the nodule echogenicity without change in size. The nodule had become hypoechoic, heterogeneous and well-defined with grade 2 vascularity. FNA revealed a poorly differentiated malignant spindle cell neoplasm, similar to biopsies of other metastatic sites, supporting a diagnosis of metastatic high grade sarcoma. The patient underwent a right thyroidectomy; pathology revealed a 4.1 cm metastatic sarcoma with multifocal angioinvasion with tumor present at the surgical margin. Follow-up neck ultrasounds showed no evidence of local recurrence, while the patient was receiving chemotherapy for pulmonary metastases. The patient died 3 years later due to a massive pulmonary embolism.

Conclusion: To our knowledge, this is the first report of a lower extremity leiomyosarcoma metastatic to a benign thyroid nodule. Although metastasis of an extra-thyroidal malignancy to a pre-existing benign thyroid nodule is very rare, patients with thyroid nodules and a history of malignancy should have regular surveillance of the nodule by ultrasound, and any changes in the nodule features concerning for malignancy should be evaluated with FNA of the nodule.

1. Chung, A. Y., Tran, T. B., Brumund, K. T., Weisman, R. A., & Bouvet, M. (2012). Metastases to the thyroid: a review of the literature from the last decade. *Thyroid*, 22(3), 258-268.

Reproductive Endocrinology

BASIC MECHANISMS IN REPRODUCTION: FROM BEGINNING TO END

Modeling Uterine Disorders Utilizing Adult Uterine Stem Cells

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Endometriosis and uterine fibroids (leiomyomas) are benign gynecological disorders affecting 5-15% of women of reproductive age. They cause a wide range of symptoms including