

larger than tumors from CD-fed mice, suggesting obesity promotes tumor growth. To investigate how obesity promotes tumor aggression, we dissociated the tumors from CD- and HFD-fed mice and plated isolated tumor cells in tumorsphere and invasion assays to test for cells with cancer stem-like cell (CSC) properties. Tumor cells from HFD-fed mice demonstrated increased tumorsphere formation and increased capacity for invasion compared to tumor cells from CD-fed mice, suggesting that obesity selects for tumor cells with CSC properties. Next, to address how obesity impacts the tumor microenvironment, we evaluated tumor necrosis and blood vessel formation through CD31 staining. Tumors from HFD-fed mice had significantly less necrosis and greater CD31 staining than those from CD-fed mice, suggesting that obesity promotes tumor angiogenesis. Since obesity promotes chronic, macrophage-driven inflammation within adipose tissue of the mammary gland, we stained tumors for the macrophage marker, F4/80. As with obese mammary glands, tumors from HFD-fed mice had significantly greater macrophage recruitment than tumors from CD-fed mice, together suggesting that obesity alters the tumor microenvironment. To determine how obesity stimulates tumor angiogenesis, we performed an *in vitro* assay by culturing dissociated tumor cells from HFD or CD-fed mice alone or with macrophages. Conditioned media (CM) isolated from tumor cells from HFD-fed mice cultured with macrophages enhanced the ability of endothelial cells to form networks *in vitro*. In contrast, CM from HFD tumor cells alone, macrophages alone, or those from CD-fed mice did not promote network formation. Together, these results suggest that cooperation between macrophages and tumor cells from HFD-fed mice promotes angiogenesis. Next, to investigate how macrophages and tumor cells interacting in obesity, we depleted macrophages using anti-F4/80 antibodies in CD-fed and HFD-fed tumor-bearing mice. In HFD-fed mice, macrophage depletion significantly reduced tumor volume and CD31 staining while increasing tumor necrosis compared to controls. Obesity promotes interactions between tumor cells and macrophages to enhance tumor angiogenesis and progression.

Thyroid

THYROID NEOPLASIA AND CANCER

Should Isthmic Thyroid Nodule Be Included in ACR TI-RADS Points in Predicting Thyroid Cancer?

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MON-492

Should isthmic thyroid nodule be included in ACR-TIRADS points in predicting thyroid cancer?

Background: Thyroid nodules are routinely evaluated with ultrasound. Isthmic nodules carry higher risk of malignancy (in press). Surgical studies suggest higher risk of metastasis from thyroid cancer located in isthmus region. In this study, we evaluate how adding an extra point for isthmic location to current ACR-TIRADS will affect the sensitivity and specificity to predict thyroid cancer.

Methods: We performed a subanalysis of isthmic nodules contained in a retrospectively created database of 3313 adult patients from six referral centers with confirmed benign or malignant nodules. Sensitivity and specificity were calculated using the current ACR TI-RADS scoring system and compared to a system that would add an extra point based on nodule location in the isthmus.

Results: There were 195 nodules in the isthmus (34 malignant). If a recommendation for FNA was considered a positive test result, the sensitivity and specificity would be 50% (17/34) and 61% (99/161) respectively using current ACR TI-RADS scoring. If an additional point was added the sensitivity and specificity would be 62% (21/34) and 36% (58/161) respectively. Adding the additional point would lead to detection of 4 additional malignant nodules at the cost of biopsying 41 additional benign nodules. If a recommendation for *either* FNA *or* follow-up ultrasound for 5 years was considered a positive test result, the sensitivity and specificity would be 82% (28/34) and 35% (56/161) respectively using current ACR TI-RADS scoring. If an additional point was added the sensitivity and specificity would be 94% (32/34) and 15% (24/161) respectively. Adding the additional point would lead to detection of 4 additional malignant nodules at the cost of either biopsying or following 32 additional benign nodules.

Conclusions: Isthmic nodules are more likely to be malignant than nodules in other locations. When using the ACR TI-RADS, adding a point for isthmic nodules improves detection of cancer with a moderate increase in the rate of FNA and follow-up of benign nodules. Given the higher risk of extra thyroidal extension and nodal metastases for isthmic cancers, this tradeoff between sensitivity and specificity may be acceptable and should be considered when dealing with nodules in the isthmus.

Keywords: thyroid nodule, ACR TI-RADS, location, isthmus, thyroid cancer

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Non-Classical POR Deficiency as a Cause of Menstrual Disorders & Infertility

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SAT-010

P450 oxidoreductase deficiency (PORD) is an autosomal recessive disease caused by bi-allelic mutations of the *POR*

gene. It is responsible for decreased activity of several P450 enzymes including CYP21A2, CYP17A1 and CYP19A1 that are involved in adrenal and/or gonadal steroidogenesis. PORD is typically diagnosed in neonates and children with ambiguous genitalia and/or skeletal abnormalities. Adult-onset PORD has been very seldom reported and little is known about the optimal way to investigate and treat such patients. In this series, we report five women aged 19-38 years, who were referred for unexplained oligo-/amenorrhea and/or infertility. Genetic testing excluded 21-hydroxylase deficiency (21OH-D), initially suspected due to increased 17-hydroxyprogesterone (17-OHP) levels. Extensive phenotyping, steroid profile by mass spectrometry, pelvic imaging and next-generation sequencing of 84 genes involved in gonadal and adrenal disorders were performed in all patients. *In Vitro* Fertilization (IVF) followed by frozen embryo transfer under glucocorticoid suppression therapy was performed in two patients. All patients had oligomenorrhea or amenorrhea. None had hyperandrogenism. Low-normal serum estradiol (E2) and testosterone levels contrasted with chronically increased serum progesterone (P) and 17-OHP levels, which further increased after ACTH administration. Despite excessive P, 17OH-P and 21-deoxycortisol rises after ACTH stimulation suggesting non-classic 21-hydroxylase deficiency, *CYP21A2* sequencing did not support this hypothesis. Basal serum cortisol levels were low to normal, with inadequate response to ACTH in some women, suggesting partial adrenal insufficiency. Pelvic imaging revealed bilateral ovarian macrocysts in all women. All patients were found to harbor rare bi-allelic *POR* mutations classified as pathogenic according to American College of Medical Genetics standards. IVF was performed in two women after retrieval of a normal oocyte number despite very low E2 levels during controlled ovarian hyperstimulation. Frozen embryo transfer under glucocorticoid suppression therapy led to successful pregnancies. These observations suggest that diagnosis of PORD must be considered in infertile women with chronically elevated P and 17OH-P levels and ovarian macrocysts. Differentiation of this entity from non-classic 21-hydroxylase deficiency is important, as the multiple enzyme deficiency requires a specific management. Successful fertility induction is possible by IVF, providing that P levels be sufficiently suppressed by glucocorticoid therapy prior to implantation.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

Durable CYP21A2 Gene Therapy in Non-Human Primates for Treatment of Congenital Adrenal Hyperplasia

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OR25-01

Severe Congenital Adrenal Hyperplasia (CAH) is most commonly caused by genetic defects in the *CYP21A2* gene,

which leads to a deficiency of 21-hydroxylase enzyme and disruption in the biosynthesis of Adrenal corticosteroids. Despite treatment with corticosteroids, patients remain at significant risk for adrenal crisis, experiencing a 3-fold higher mortality rate than age matched controls. They also suffer from significant infertility, bone, metabolic, and cardiovascular disease, and hyperandrogenism in women leading to genital abnormalities, hirsutism, and other complications. We are developing an AAV5- based gene therapy (BBP-631) that will provide a functional copy of the *CYP21A2* gene to the adrenal glands of CAH patients. To determine the durability of this therapy we treated cynomolgus monkeys with increasing doses of BBP-631 via intravenous injection. At 4-, 12- and 24-weeks post treatment, expression of hCYP21A2 mRNA and vector genome copies (VGC) in the adrenals and other peripheral tissues was measured. VGC was present in the liver and adrenals at 4 weeks, with durable detection through 24 weeks and total vg levels were dose dependent. hCYP21A2 RNA expression in adrenal and liver tissues was also dose dependent and continued to increase from 4 weeks through 12 weeks. There were no adverse safety signals in any of the treated animals. This data combined with efficacy data of BBP-631 in a *Cyp21*^{-/-} mouse model supports our continued clinical development of BBP-631 as a treatment for congenital adrenal hyperplasia.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Glucose Metabolism in Acromegaly Patients Resistant to First Generation Somatostatin Receptor Ligands Treated with Pegvisomant And/Or Pasireotide Lar

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MON-311

Introduction: Acromegaly (Acro) is a systemic disease characterized by high growth hormone (GH) and insulin like growth factor-I (IGF-I), insulin resistance, glucose intolerance (IGT) and higher diabetes mellitus (DM) risk in 15% - 38% of patients (pts). Moreover, different medical therapies of Acro are reported to have variable effects on glucose metabolism. An association between blood glucose (BG) and serum IGF-I levels in patients with DM and Acro has been suggested, while IGF-I levels and hemoglobin A1c (HbA1c) correlation is still controversial because of the multifactorial influence. Study aim: to investigate glucose metabolism in pts with Acro resistant to 1st gen somatostatin receptor ligands (SRLs) treated with Pegvisomant (Peg) or Pasireotide LAR (Pasi). **Patients and Methods:** Retrospective, international, multicenter study; consecutive pts enrolled according to following inclusion criteria for at least 6 consecutive months: (1) resistant to 1st gen