SAT-386

Background: More than 95% of patients with primary hyperparathyroidism will be cured with the initial operation by an experienced surgeon. However, localization of hyperparathyroid recurrences, especially after extensive surgery becomes challenging. For patients with transplanted parathyroid glands into the forearm, there may be utility in bilateral arm serum PTH testing to help with localization.
Clinical Case:
A 65-year-old woman presented to the clinic with primary hyperparathyroidism in 2008. After a localization study, she had a partial parathyroidectomy but continued to have persistent biochemical hyperparathyroidism despite negative localization studies. She was then referred to another institution for further studies. Follow up Sestamibi scans were negative but 4D-CT scans assisted in localizing the presence of a superior parathyroid gland adenoma which was later removed in 2011. During this time, the left inferior parathyroid gland was auto-transplanted into the left forearm. Again, her calcium and PTH levels rose despite negative Sestamibi scans showing no abnormalities in post-operative beds or in the forearm. Review of previous labs revealed elevated PTH levels in the ranges of 80-110 pg/mL since 2012-2019. The patient's most recent PTH was 2408 pg/mL. At that point, the decision was made to repeat the labs on the left and right forearms simultaneously and labs showed PTH levels of 1283 pg/mL and 118 pg/mL, respectively. Repeat Sestamibi scan following these labs demonstrated evidence of increased radiotracer uptake in the region of the prior transplanted parathyroid tissue with no neck uptake concerning for hyperparathyroidism due to auto-transplanted hyperplastic tissue.
Conclusion:
This case demonstrates the utility of bilateral arm serum PTH testing in the evaluation of recurrent hyperparathyroidism in patient's status-post parathyroid auto-transplantation.

Adrenal

ADRENAL CASE REPORTS I

Is Doxazosin the Right Choice for Preoperative Management of Pheochromocytoma in Pregnancy?

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SAT-211

Pheochromocytoma (PCC) in pregnancy is a very rare condition, with a reported incidence of less than 0.2 per 10.000 pregnancies (1), having fetal and maternal mortality of 50% if untreated (2). Choosing between selective vs. nonselective alpha blockers as preoperative management in pregnancy is controversial.
We report a case of a 39-year-old female having episodes of nervousness, hand tremors, palpitations, diaphoresis, and headaches since 2012; she also had a history of multiple miscarriages and uncontrolled hypertension(HTN) since 2018. In 2019, she was found to have plasma metanephrines 690pg/mL (0-62) and plasma normetanephrine of 3803pg/mL(0-145). Repeat labs showed: plasma metanephrines 2.071pg/mL(0-62), normetanephrine 6.289pg/mL(0-145), norepinephrine 4.268pg/mL(0-874), epinephrine 555pg/mL(0-62). CT abdomen showed a 6.2x5.1x6.4cm left adrenal mass, with 44 Hounsfield units and less than 50% of washout. She was started on Doxazosin 2mg/d, which eventually was increased to 6mg/d with optimal blood pressure (BP) control. After her preoperative workup, she was found to be 7 weeks pregnant. OB-GYN recommended left adrenalectomy before 14 weeks gestation. She had left open adrenalectomy, with normal range postoperative BP, off of antihypertensive medications.
The diagnosis of PCC in pregnancy should be considered in the setting of paroxysmal HTN, with no proteinuria, episodic palpitations, diaphoresis, facial flushing, and orthostatic hypotension. Anterior adrenalectomy early in pregnancy is recommended. The increased intraabdominal pressure, fetal movements, uterine contractions, delivery process, and abdominal surgical intervention can trigger the catecholamine release by the PCC, which could lead to placental abruption and miscarriage; and the rebound hypotension may lead to severe hypoxia, causing fetal demise (2). Definitive preoperative treatment between selective vs non-selective alpha-blockers remains controversial. Phenoxybenzamine, appeared to produce better attenuation of intraoperative HTN, however, it is associated with more maternal intraoperative/postoperative hypotension, and reflexive tachycardia. It crosses the placenta and accumulates in the fetus, increasing the risk of neonatal hypotension and respiratory depression (3,4,5). On the other hand, Doxazosin, can be displaced by high levels of catecholamines, but it is less associated with intraoperative/postoperative hypotension (6,7), with no reports of neonatal hypotension, and respiratory depression. Due to the lack of presynaptic a2-adrenoceptor blockade there is less reflex tachycardia, reducing the use of Beta-blockers (8). Doxazosin seems to be a safe, affordable alternative for preoperative management of PCC in pregnant patients.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

Targeting Glutamate Metabolism and Signaling in ER+, Endocrine Therapy-Resistant Breast Cancer

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SAT-119

Estrogen receptor-positive (ER+) breast cancer is the most commonly diagnosed form of this malignancy. Aromatase inhibitors and selective estrogen receptor modulators or degraders (SERMS, SERDs) can be highly effective in treating ER+ breast cancer, but *de novo* and acquired resistance to these interventions is a persistent clinical problem. Endocrine therapy resistant breast cancer cells rewire their metabolism to support cellular demands associated with rapid proliferation and/or increased invasion

and metastasis. An important feature of this metabolic flexibility is conversion of glutamine to glutamate, an amino acid integral to protection of cells from oxidative stress. Consistent with this, we show multiple cellular models of ER+, endocrine resistant breast cancer cells markedly increase glutamate release and upregulate expression of essential glutamine/glutamate metabolic enzymes and transporters, including the glutamate/cystine antiporter xCT, glutamate dehydrogenase (GLUD1/2), and/or the glutamine importer SLC1A5. Riluzole (RIL) is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS), and has several proposed mechanisms of action, including suppression of glutamate release and increased glutamate uptake. We show ER+, endocrine responsive and resistant breast cancer cells are growth-inhibited by RIL. This is due to an increase in cell death, particularly in endocrine resistant breast cancer cells, and cell cycle arrest. Interestingly, histologic subtype confers a different cell cycle arrest profile, with invasive ductal cancer (IDC) models arresting in G1 but invasive lobular cancer (ILC) models arresting in G2/M. Isobologram analysis of RIL plus SERMs or SERDs shows additive-to-synergistic activity in a subset of ER+ cell line models, and preliminary studies show combination activity in patient-derived explants (PDEs). Mechanistically, we tested whether signaling through metabotropic glutamate receptors (mGluRs, GRMs) and/or cystine import contribute to RIL's growth-inhibitory phenotype. Antagonists of mGluRs/GRMs don't phenocopy the effects of RIL, suggesting extracellular glutamate signaling through these receptors is not a key mechanism. Rescue experiments with β-mercaptoethanol to promote cystine uptake through transporters other than xCT show partial reversal of RIL-mediated cell cycle arrest in some cells, suggesting xCT may contribute to RIL-induced growth inhibition. In summary, we show RIL may be a viable addition to endocrine therapy in ER+ breast cancer. Ongoing studies will test additional mechanism(s) by which RIL may attenuate the growth of ER+ breast cancer models *in vitro*, including inhibition of protein kinase C and casein kinase 1 delta. We are further testing RIL efficacy alone and in combination with a SERD in primary tumors and lung metastases in a ER+ patient-derived xenograft (PDX) model.

Diabetes Mellitus and Glucose Metabolism

GESTATIONAL DIABETES, DIABETES IN PREGNANCY, AND IN UTERO EXPOSURES

Profiling of Activation Patterns of Placental mTOR in Pregnancies Complicated by Gestational Diabetes Mellitus

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SUN-635

The mammalian target of rapamycin (mTOR) couples' energy and nutrient abundance to cell growth and is critically involved in the onset and progression of diabetes, cancer and ageing. Placental mTOR is involved in nutrient sensing and transfer to the fetus; animal models suggest that placental mTOR is upregulated in pregnancies complicated by hyperglycaemia (1). In this study we investigated expression patterns and activation of placental mTOR and possible effects of gestational diabetes (GDM). Our study consisted of GDM-mothers (n=28) and their offspring and ii) mothers (n=33) with normal pregnancies (non-GDM) and their infants. Total and phospho-mTOR (Ser2448) expression were determined in placental biopsies using either immunoblotting and immunohistochemistry (IHC) analysis. Newborn anthropometric parameters were also determined at delivery. GDM pregnant women presented with higher fasting glucose levels than non-GDM (98.12±22.82mg/dL; 73.61±9.89mg/dL; $p<0.001$). No significant difference was found in birth weight or baby length between GDM and non-GDM infants. IHC analysis showed that both total and activated mTOR were predominantly expressed in trophoblasts and to a lesser extend in syncytiotrophoblasts, in both GDM and non-GDM placentas. GDM placentas exhibited a higher mTOR H-score (2) compared to non-GDM ($p<0.012$), and WB analysis showed a higher phosphor-mTOR signal intensity ($p=0.047$) in the same group, most likely due to increased total mTOR expression. mTOR expression was also increased in both GDM syncytiotrophoblasts and endothelial cells compared to non-GDM ($p<0.001$) whereas a reduced signal was detected in stromal phospho-mTOR ($p=0.004$). No difference was found in trophoblasts or endothelial cells between the 2 study groups suggesting that activation of this kinase is tightly regulated and is relatively independent of changes in total kinase levels. Interestingly bivariate correlation analysis identified an extensive network of significant associations in the expression levels of total, phosphor-mTOR and P/T mTOR between trophoblasts, stroma, endothelial and syncytiotrophoblastsin control placental biopsies; this network was significantly disrupted in GDM placentas, identifying a disheveled regulation of placental mTOR activity. In conclusion, placental mTOR/PmTOR expression is differentially regulated across different placental cell types and is sensitive to hyperglycaemia associated with gestational diabetes mellitus.(1)M. Castillo-Castrejon and TL. Powell. Front Endocrinol (Lausanne). 2017; 8: 306. (2) E. Lakiotaki, et al., Scientific Reports 2016; 6, 21252.

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

The Burdens of Adrenal Insufficiency: A Survey Study from Two Tertiary Care Centers in the United States

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