has been recommended to hold off on radiation therapy. She is currently taking replacement doses of hydrocortisone and fludrocortisone.
Conclusion:
In this challenging case, determination of source of ACTH hypersecretion led to an initial diagnosis of breast cancer. Primary breast carcinoma with neuroendocrine differentiation has been reported to show significant overlap in pathology with NET metastatic to the breast[1]. However, worsening of the CS in this case led to consideration of an alternative diagnosis, resulting in diagnosis of an ACTH producing NET metastatic to the breast. Prior to chemotherapy, she underwent BLA, which may lower morbidity and mortality associated with ACTH-dependent CS[2], particularly given plan for further chemotherapy.
Reference:
1. Mohanty SK, Kim SA, DeLair DF, et al. Comparison of metastatic neuroendocrine neoplasms to the breast and primary invasive mammary carcinomas with neuroendocrine differentiation. *Mod Pathol*. 2016;29(8):788-798. doi:10.1038/modpathol.2016.69.2.
2. Morris LF, Harris RS, Milton DR, et al. Impact and timing of bilateral adrenalectomy for refractory adrenocorticotropic hormone-dependent Cushing's syndrome. Surgery. 2013;154(6):1174-1183; discussion 1183-1184.

Reproductive Endocrinology
FEMALE REPRODUCTION: BASIC MECHANISMS

Estrogen-Responsive and -Unresponsive Gene Expressions Promoted by Enhancers Specifically Hypomethylated in Endometriotic Cells May Become a Molecular Marker in Endometriosis Lesions

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MON-008

Background: Endometriosis is an estrogen-dependent, inflammatory disease, and the role of estrogen is obvious because the symptoms associated with endometriosis often disappear after menopause, and GnRH agonists or progestin relieve the pelvic lesions and endometriosis-associated pain. However, there are limitations to these treatments that target the estrogen reduction in endometriotic lesions. We sought to define an aberrant gene expression derived from an epigenetic background in endometriosis.**Objective**: In the hope of overcoming the limitations of endocrine treatments in endometriosis, we examined estrogen receptor (ER)-dependent and -independent gene expressions promoted by active enhancers specifically hypomethylated in endometriotic cells.
Patients: Institutional Review Boards approved this project. We obtained the informed consent from all patients. The chocolate cyst lining in ovaries of patients with endometriosis was the source of endometriotic tissue. As the control, the eutopic endometrial tissues were obtained from uteri of premenopausal women who had uterine leiomyoma.**Methods**: Stromal cells were prepared from endometriotic and endometrial tissues. Gene expression was examined using RT-PCR. The potential function of hypomethylated gene sequence as an active enhancer was evaluated by ChIP analysis using anti-H3K4me1 and anti-H3K27ac antibodies and eRNA expression analysis. Using ChIP-seq and ChIA-PET analysis *in silico,* ER-specific loci within gene bodies and the up- and downstream regions were extracted. ER-dependent gene expression was examined using estradiol or SERM.**Results:** ER expression in endometriotic cells.1) Relative expression of ERα mRNA was estimated to be one tenth of that in endometrial cells. 2) Relative expression of ERβ1 mRNA was 40-fold higher than that in endometrial cells, which is at a comparable level of the ERα. 3) ERβ2 mRNA expression was at a comparable level of the ERβ1. From our DNA methylation and gene expression analysis, 6 genes were selected and classified into 3 categories: estrogen-responsive genes with specific methylation (*ESR1* and *ESR2*) or without any methylation (*TGFα* and *GREB1*), and estrogen-unresponsive but upregulated genes depending on specific hypomethylation (*GATA6* and *CYP19*). 4) ChIP-seq and ChIA-PET analysis *in silico* suggested the presence of ER-specific loci within gene bodies and the up- and downstream in estrogen-responsive genes. 5) ChIP and eRNA expression analysis predicted active enhancer regions both in estrogen-responsive and -unresponsive genes. 6) In response to estrogen, *TGFα* and *GREB1* expressions were upregulated, but *ESR1 and ESR2* showed marginal responses.**Conclusion**: We focused on estrogen-responsive and -unresponsive genes linked to the epigenetic environment of endometriotic lesions, and revealed a facet of gene expression in endometriotic cells.

Reproductive Endocrinology
FEMALE REPRODUCTION: BASIC MECHANISMS

The Direct Effect of Kisspeptin on Human Ovarian Granulosa Cells to Regulate Steroidogenesis

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MON-012

Kisspeptin has a central role to stimulate the hypothalamic-pituitary-gonadal (HPG) axis. Furthermore, a previous study has suggested that kisspeptin might have a peripheral role in follicular development (1). This study aimed to 1) explore the effect of kisspeptin on *CYP19A1* (aromatase) mRNA expression in human granulosa cells and aromatase concentrations in the supernatant; and 2) investigate the effect of kisspeptin on *FSHR* mRNA expression in human granulosa cells. In this study, human granulosa-like tumor cell line (KGN) (n=3) was incubated for 24 hours with FSH (10^{-8} M); FSH with IGF-1 (10^{-8} M); different doses of kisspeptin including 1, 10, 100, 1,000, and 10,000 nM; FSH with different doses of kisspeptin; and FSH with IGF-1 together with different doses of kisspeptin. FSH treatment alone or FSH with IGF-1 did not increase *CYP19A1* mRNA expression when compared to control. Interestingly, kisspeptin treatment at the doses of 100 nM (P=0.028), 1,000 nM (P=0.005),

and 10,000 nM (P=0.009) in the presence of FSH together with IGF-1 enhanced *CYP19A1* mRNA expression when compared with control. Furthermore, FSH or FSH with IGF-1 or FSH with all doses of kisspeptin or FSH with IGF-1 together with all doses of kisspeptin increased aromatase concentrations in the supernatant when compared to control (P<0.01 all). Surprisingly, kisspeptin at the dose of 10,000 nM with FSH or FSH together with IGF-1 statistically increased aromatase concentrations in the supernatant when compared with FSH treatment alone or FSH with IGF-1 treatment (P<0.01 all). *FSHR* mRNA expression was comparable between control and all treatments. As a result, kisspeptin combined with FSH and IGF-1 could enhance *CYP19A1* mRNA expression in human granulosa cells and the high dose of kisspeptin (10,000 nM) might be able to augment aromatase secretion in the supernatant. These results suggest that kisspeptin might enhance aromatase expression and secretion, which probably leads to enhance estrogen synthesis. Further studies regarding kisspeptin treatment on estrogen synthesis or secretion in human granulosa cells should be confirmed. **Reference:** (1) Fernandois D, et al. J Endocrinol. 2016;228(3):161-70.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Identification of Novel Mirnas Found to Be Differentially Expressed Between ATA Risk Stratification Groups in Papillary Thyroid Carcinoma

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SUN-119

Abstract: The study of miRNAs in PTC has shown that these molecules can help in the diagnosis, prognosis and also as therapeutic candidates [1]. miRNAs are known to be differentially expressed in PTC compared to non-cancerous tissue and a few studies have shown association with some clinico-pathological features. However, little is known regarding their expression in relation to risk of disease progression. In this study, we examined the expression of miRNAs in patients diagnosed with PTC in association with risk of disease recurrence and/or persistence.

Patients were classified by three endocrinologists to either high (H) or low (L) risk according to ATA Risk Stratification. PTC tissue was micro-dissected from Formalin Fixed Paraffin Embedded (FFPE) tissue for analysis. OPenArray analysis showed that 21 miRNAs were differentially expressed in H-L groups (n=4/grp). qRT-PCR was used to confirm these differences in a larger cohort of PTC (H=46; L=58). This comparison also included comparisons between cancer and normal tissue and investigation of miRNAs known to be differentially expressed (i.e miRNAs 222, 221 and 146b). All analysis was performed in Rstudio using ΔΔCt relative to expression of miR-16 which was not altered by PTC.

By qRT-PCR, only 3 of the 21 miRNAs identified by OpenArray analysis, were differentially expressed in H vs L risk (each P<0.05). These miRNAs are known to be involved in cancer progression pathways but have not been reported in PTC. Individual Receiver Operating Characteristic (ROC) curve analysis of these 3 miRNAs had AUC as follows (miR 1: 0.62, miR 2: 0.62, miR 3: 0.64,) and when analyzed together, the AUC model was improved (AUC=0.76). Examination of cancer vs normal tissue confirmed higher expression miR-146b, miR-221 and miR-222 (each P<0.05). However, these miRNAs were not differentially expressed when H vs L risk were analysed.

In this study, we identified 3 miRNAs with potential utility for the stratification of patients into those with H or L risk disease recurrence/persistence. As the current ATA 3-tiered system used is still a reflection of the continuum of risk that patients have, whether these 3 miRNAs may have the utility to further stratify those in the intermediate group remains to be investigated.

Reference: 1.

Ramírez-Moya, J. and P. Santisteban, *miRNA-Directed Regulation of the Main Signaling Pathways in Thyroid Cancer.* Frontiers in Endocrinology, 2019. **10**: p. 430.

Thyroid

THYROID DISORDERS CASE REPORTS II

A Rare Case of Pretibial Myxedema Preceding Graves' Hyperthyroidism

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SAT-471

Introduction:

Pretibial myxedema, also known as thyroid dermopathy, is typically seen as a manifestation of long-standing Graves' disease. We report a rare case of pretibial myxedema as the initial presentation of Graves' disease in a patient without ocular or overt hyperthyroid symptoms.

Case:

The patient is a 68 year old male with a past medical history of type 2 diabetes and hypertrophic cardiomyopathy, presenting with a one year history of a mildly pruritic, violaceous plaque of his left shin. He was referred to Dermatology Clinic, and biopsy came back as pretibial myxedema. Of note, his thyroid function studies were normal 6 months prior, and he had no symptoms of active thyroid disease at presentation. Additionally, he did not have any ocular abnormalities on exam. Upon repeat laboratory studies, he had low but detectable TSH, normal