Abstract citation ID: bvac150.134

Adrenal

ODP055

The methylation pattern of a unique Bilateral paraoverian Adrenal Rest Tumor in a girl with Nicotinamide Nucleotide Transhydrogenase mutation

Ranit Cahn, MD, David Zangen, MD, Espen Mendelsohn, MD, Natan florsheim, bSC, Benjamin P. Berman, PhD, Abdulsalam Abu-Libdeh, MD, and Eran Lavi, MD

Background: Patients with NNT (Nicotinamide Nucleotide Transhydrogenase) gene mutations, a rare cause of glucocorticoid and mineralocorticoid deficiency require hormone replacement therapy. Adrenal Rest Tumor (ART) in females, reported so far only in noncompliant patients with congenital adrenal hyperplasia and elevated ACTH levels, is very rare (<20 cases world-wide). This study characterizes the pathophysiology, the molecular ontogeny and methylation analysis of a unique ART in a female with adrenal failure due to the G200S mutation in NNT Clinical presentation and Method: A 15-year-old girl, with homozygous G200S NNT-mutation followed for adrenal insufficiency reappeared to follow-up with severe virilization and elevated serum testosterone (28.3 nmol/l) and ACTH (> 1500 pmol/l). Pelvic MRI and Ultrasound demonstrated one sided paraovarian round tumor with pathological vascularization. Laparoscopic exploration revealed bilateral para ovarian mesosalpinx masses involving the serosa of the Fallopian tube, (3 and 1 cm in diameter). The testosterone level normalized within one day after surgical removal of those masses (0.2 nmol/l). **Results:** Histopathology demonstrated a pattern of adrenal rest tissue with strong intracellular positive staining for adrenal markers such as SF-1, calretinin, MART1, inhibin and the pituitary marker ACTH. The staining for ovarian characteristic markers such as PAX 8 was negative. Studying mRNA extracted from the tissue by RT-PCR revealed the positive Gene expression of Cyp17a1, Cyp21a2 and Mc2r cDNA but not Pomc suggesting adrenal but not pituitary origin of the tissue. We further profiled the epigenomic profile of several adrenal rest tumors from both ovarian and testes origins using the Infinium Methylation EPIC array. We characterized the adrenal-specific features by comparing the tumors from the two different originating sites to published methylation array data on healthy adrenal tissue. We further investigated cancer-specific methylation changes to identify activated cancer pathways, and used the methylation arrays to identify somatic copy number alterations. Finally, we analyzed the likely developmental origin of these tumors by comparing to published methylation array data of developmental and adult reproductive tissues. **Conclusion:** This study exemplifies severe virilization that resulted from a unique and rare type of ART in ovarian related tissue that was caused by incompliance to treatment in a patient with NNT gene mutation. The laparoscopic surgical findings indicate that imaging techniques may be insufficient in identification of such rest tumors and call for laparoscopy when clinical findings are suggestive. An early detection of this tumor could preserve fertility. Using histopathology markers cDNA studies

and epigenomic profiling by methylation studies, our study shows for the first time that female ART originates from adrenal cells. The growth of a functional androgen producing "tumor" indicates that functional NNT protein is NOT required for androgen synthesis in contrast to glucocorticoids and that a zona reticularis similar tissue in ART is responsive to ACTH stimulation.

Presentation: No date and time listed