cyclic Cushing syndrome caused by an intestinal neuroendocrine tumour (NET) detected by 68GA-DOTATATE PET-CT, despite functional tests that were indicative of pituitary Cushing disease. Clinical Case A 53-year old man was admitted to outpatient clinic because of muscle weakness. His phenotype and clinical findings (progressively worsening upper and lower limb weakness, emotional disturbances, easy bruising, a Buffalo hump, prediabetes and leucocytosis) led to the diagnosis of Cushing syndrome. Initial laboratory tests established the diagnosis with an abnormal diurnal cortisol and ACTH secretion (night cortisol F: 22.1µg / dl), absence of suppression with dexamethasone 1mg and increased free urinary free cortisol 24h (243.5µg /24h). Abdominal CT scanning revealed a left-sided adrenal adrenocortical adenoma 1.5 mm in max diameter. Pituitary MRI and somatostatin scintigraphy were normal. Low dexamethasone suppression test was indicative of Cushing (F: 14µg / dl) followed by a combined CRH stimulation test during bilateral inferior petrosal sinus sampling. Pituitary / peripheral ACTH ratio pre-infusion of CRH and 3 min after CRH infusion was compatible with right-sided pituitary origin of ACTH hypersecretion. Pending the results of the laboratory, the patient showed a remission of his symptoms along with a laboratory-confirmed recession of active hypercortisolaemia (LDDST test), and this led to the suspicion of periodic Cushing syndrome. The patient was followed with clinical and laboratory examinations weekly, with recurrence of symptoms 2 months later followed by a new remission 3 months later. A PETGA CT SCAN with 68GA-HA-DOTATATE was performed, which showed an increased uptake of the radioisotope in the small intestine. A surgical excision of the affected small bowel region was performed according to the guidelines for intestinal NETs. Histology confirmed the existence of a well-differentiated neuroendocrine neoplasm of the small intestine of 1.1 cm diameter, grade 1 (WHO 2010). Immunophenotype was positive for serotonin and ACTH. Postoperatively, the patient showed a complete remission of symptomatology and regression of hypercortisolaemia over a 18-month period. Follow-up abdominal MRI and 68GA-HA-DOTATATE revealed no pathological findings. Conclusion: Our patient is the first case of ectopic Cushing disease caused by intestinal NET. The differential diagnosis between pituitary and ectopic Cushing syndrome due to ACTH or CRH hypersecretion is not easy and frequently complicated by the periodicity of the disease. In patients with no visible pituitary lesions on MRI we suggest further investigation for ectopic ACTH- driven Cushing syndrome.

Thyroid

THYROID NEOPLASIA AND CANCER

Prospective Evaluation of Patients with Encapsulated Classical Variant of Papillary Thyroid Cancer and Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP): Have They A Similar Prognosis?

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Background: Our previous retrospective study demonstrated that the absence of tumor capsule or, if present, its invasion were independent risk factors for the persistence of the disease (OR 6.75, CI 1.97-23.08 and OR 7.89, CI 1.78-34.94, respectively) in papillary thyroid cancer (PTC). This data was confirmed also analyzing separately the most frequent PTC variants [follicular variant (FVPTC) and classical variant (CVPTC)]. Moreover, we demonstrated that the absence of tumor capsule was significantly more frequent in FVPTC *BRAF* V600E mutated than FVPTC wild-type for *BRAF* gene or with *rare-BRAF* mutations (e.g., *BRAF* K601E, *BRAF* V600_K601delinsE). These data confirmed the importance of the integrity of the tumor capsule in FVPTC which led in 2016 to the definition of a new thyroid neoplasm entity named NIFTP. According to these retrospective data, we have assumed that the integrity of the tumor capsule in CVPTC could have a prognostic role similar to that confirmed in the NIFTP group.
Methods: we have prospectively collected data of patients (pts) underwent total thyroidectomy or lobectomy for encapsulated-CVPTC (E-CVPTC) or NIFTP. In both cases the tumor was accurately analyzed by the pathologists according to the criteria used for the NIFTP (in particular with one capsule sample every 1 mm). All pts performed at least one clinical control and neck US within 6 months from surgery.
Results: From January 2018 to June 2019, 144 E-CVPTC and 177 NIFTP were prospectively collected. 83/144 (57.6%) E-CVPTC and 106/177 (59.8%) NIFTP cases were included. The others were excluded due to the presence of other thyroid tumors associated in the same gland. No differences in epidemiological and pathological features were found between E-CVPTC and NIFTP except for the tumor size, significantly bigger in NIFTP than E-CVPTC [22±16mm (2-68) *vs* 8±11mm (1-80), p<0.00]. A significantly higher rate of NIFTP' pts underwent lobectomy respect to E-CVPTC pts (34%*vs*14.5%, p=0.02). After a mean of 9 months of follow-up all pts had an excellent response according to ATA guidelines.
Conclusions: These prospective data demonstrated that NIFTP and E-CVPTC have a similar clinical behavior in a short-term follow-up, thus suggesting that the presence of an intact tumor capsule is predictive of a good outcome. A longer follow up is needed to confirm these initial interesting findings.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

The Effect of Hypertriglyceridemia on Triple Negative Breast Cancer Progression

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SAT-137

Obesity is associated with increased cancer risk and cancer-associated mortality[1,2]. Hypertriglyceridemia (HTG), a component of the metabolic syndrome which frequently co-exists with obesity, has been associated with increased breast cancer risk and mortality in triple negative breast cancer (TNBC)[3,4]. To determine if HTG is causally related to enhanced TNBC progression in the absence of other obesity-associated characteristics, TNBC growth and metastasis in a mouse model of HTG was examined. Mice overexpressing human apolipoprotein C3 (AC3) were backcrossed onto FVB/N background and crossed with recombination-activating gene 1 (Rag1) knockout mice to generate immunodeficient HTG mice. AC3 mice relative to wild-type (WT) littermates showed a 20-fold higher circulating triglycerides ($p < 0.0001$) and elevated very low density lipoprotein (VLDL) cholesterol ($p = 0.001$). No differences in body weight, body composition, blood glucose or plasma insulin levels were observed between the two groups, allowing for investigation on the influence of HTG on TNBC without confounders such as hyperinsulinemia or hyperglycemia. AC3 mice orthotopically implanted with the mouse mammary tumor cell line, Mvt1, showed both increased tumor growth (AC3 vs WT: 1157.0 ± 84.2 vs 707.2 ± 58.6 mm^3, $p = 0.0009$) and lung metastasis (AC3 vs WT: 57.3 ± 3.0 vs 32.9 ± 5.3 mm^3, $p = 0.001$) relative to WT mice. Immunodeficient Rag1/AC3 mice likewise, showed increased tumor growth compared to WT controls when implanted with human TNBC MDA-MB-231 cells (AC3 vs WT: 363.2 ± 113.9 vs 92.95 ± 16.2 mm^3, $p = 0.038$). To investigate how HTG affects tumor lipid metabolism, serum and tumors from both groups were analyzed by liquid chromatography/mass spectrometry. Total alkyl-acyl, di-acyl-phosphatidylcholines and sphingomyelin concentrations were higher in the serum of AC3 mice relative to WT. In contrast, no overall difference in tumor phospholipid or acylcarnitine content was noted between AC3 and WT mice, suggesting no difference in fatty acid oxidation in the setting of HTG. Mvt1 tumors from AC3 and WT mice were analyzed by RNA sequencing. Decreased expression of genes associated with cholesterol synthesis (Fdft1, Pvmk, Acss2) were found in tumors from AC3 mice. Tumors from AC3 mice also showed decreased protein expression of LDLR, which is associated with LDL cholesterol uptake. Overall, these findings

suggest that HTG, independently of other obesity-associated characteristics such as hyperinsulinemia and hyperglycemia, leads to changes in intracellular lipid metabolism and promotes TNBC progression.

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Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of a Selective Glucocorticoid Receptor Modulator, Relacorilant, in Patients with Autonomous Cortisol Secretion Due to Cortisol-Secreting Adrenal Adenoma(s)/Hyperplasia

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Relacorilant is a highly selective glucocorticoid receptor antagonist that modulates the effects of excess cortisol without interacting with the mineralocorticoid or progesterone receptor. A Phase 2 relacorilant study in patients with endogenous Cushing syndrome (CS) demonstrated improvements in glycemic control and hypertension with no instances of drug-related hypokalemia or antiprogesterone effects.

An international, multicenter, Phase 3 clinical trial of relacorilant is currently underway to evaluate the efficacy and safety of relacorilant in CS of various etiologies with evidence of hypercortisolism documented through two independent biochemical tests and at least two clinical signs and symptoms of CS. It uses a randomized-withdrawal design after 22-weeks (22wk) of open-label treatment with relacorilant (GRACE Study: NCT03697109).

Here we introduce a double-blind, randomized, placebo-controlled study in patients with less severe CS secondary to adrenal adenoma(s) or hyperplasia. Approximately 130 eligible patients 18-80 years old with a radiologically confirmed adrenal lesion, a biochemical diagnosis of autonomous cortisol secretion and either impaired glucose tolerance/diabetes mellitus (IGT/DM) or hypertension will receive relacorilant (100 mg/day, titrated to 400 mg/day, as tolerated) or placebo over 22WK.

Biochemical criteria for entry into the study include a serum cortisol >1.8 μg/dL after dexamethasone suppression testing (DST) and low (<10 pg/dL) or suppressed morning ACTH levels. Patients must be stable on their antidiabetic and/or antihypertensive agents for at least 4 weeks prior to the first dose of relacorilant.

The primary efficacy endpoints are the between-treatment difference in change from Baseline to 22wk in AUCglucose for the IGT/DM group and mean systolic blood pressure (based on ambulatory blood pressure monitoring) for the hypertension group. Secondary endpoints include changes in weight, waist circumference, quality of life and coagulation markers. The safety analysis will be performed for all patients who received at least one dose of study drug.

This will be the first randomized, double-blind, placebo-controlled study to test if patients with adrenal autonomous hypercortisolism benefit from medical treatment.