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IntroductionAging is associated with the pathogenesis of many endocrine disorders such as cardiovascular diseases and diabetes. Cell senescence has been reported as one of their mechanisms. In addition, stress responsiveness has been reported to be associated with cell senescence. In addition, some genetic abnormalities such as mitochondrial DNA (mtDNA) damages or telomere shortening, have been detected in some endocrine disorders. Cortisol is a well-known stress-induced hormone and closely associated with aging. We previously reported that cortisol-producing adenoma (CPA) more abundantly expressed cell senescent markers such as p16 and p21 than other hormone-producing adrenocortical adenomas. However, the detailed pathophysiology of cell senescence and its association with histological features in CPAs have remained virtually unknown. Therefore, we analyzed cell senescent markers (telomere length, mtDNA copy number, mtDNA deletion and p16 and p21 immunoreactivity) and analyzed their correlation with clinicopathological factors in CPA patients. **Methods & Materials**Forty CPA cases was immunohistochemically evaluated. Twenty CPA, ten adjacent ZF and six non-functional adenoma (NFA) were examined for mtDNA abnormalities. mtDNA deletion was evaluated by nested-PCR and mtDNA copy number and telomere length were measured using real-time PCR. **Results**

p21 immunoreactivity was significantly higher in CPA than that of adjacent ZF (P=0.0001) and significantly inversely correlated with tumor size (P=0.0004). Telomere length was much longer in CPA than that in adjacent ZF(P=0.0038), and NFA (P=0.0018). mtDNA copy number of NFA was significantly higher than that of CPA and adjacent ZF (P=0.0038). mtDNA copy number of compact cells was significantly higher than that of clear cells (P=0.0432). mtDNA copy number of compact cells was positively correlated with urinary free cortisol (UFC) (P=0.0428) and plasma cortisol (F) (P=0.0609). mtDNA copy number of clear cells were inversely correlated with F (0.0497). 4977 bp mtDNA deletion was more frequently detected in CPA (54%) and in adjacent ZF (50%) than in NFA (17%).**Discussion**

Results of our present study did reveal that CPA harbored more senescent phenotype as demonstrated by abundant p16 and p21, marked telomere shortening, frequent mtDNA 4977bp deletion and relatively low mtDNA copy number, possibly caused by long-term exposure of excessive cortisol in situ compared to NFA. In addition, clear tumor cells could represent more senescent histological phenotype because of their lower mtDNA copy numbers. This is the first study to demonstrate that compact tumor cells were biologically more active than clear tumor cells and could reflect clinical cortisol biosynthesis, resulting in marked functional intratumoral heterogeneity in CPAs.

Bone and Mineral Metabolism

PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS

Safety and Efficacy of Conventional Therapy with Calcium and Activated Vitamin D in Patients with Chronic Post-Operative Hypoparathyroidism: Results of a Cross-Sectional Case-Control Study

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Introduction: Conventional therapy of chronic post-operative hypoparathyroidism (PO-HypoPT) with calcium and activated vitamin D is suboptimal and associated with several complications, including impairment of the quality of life. Aim of this study was to compare clinical, biochemical and instrumental parameters in 120 patients who underwent total thyroidectomy for differentiated thyroid cancer, 60 with PO-HypoPT (Group A) treated with conventional therapy and 60 without (Group B), matched for age and sex, followed a tertiary referral center. Matherials and methods: An "ad hoc" CRF was used to collect epidemiological, clinical (symptoms, treatment) and biochemical data (total and ionized calcium, albumin, phosphate, magnesium, calcium/phosphate product, creatinine, 25-OH vitamin D, PTH, TSH, eGFR, 24-h urinary calcium and creatinine), and renal ultrasound. Results: The median duration of PO-HypoPT was 7 years (IQR 4-13). All patients of group A were treated with calcitriol (median 0.5 μg/daily; IQR 0.5-1.0), and 33/60 (55%) were also given calcium carbonate supplementation (median 1000 mg/daily; IQR 500-1000). Hypocalcemia related symptoms were more frequent in group A (27/60 - 45%) than in group B (1/60 - 1.7%) ($p<0.01$). Total and ionized serum calcium [median 8.9 (IQR 8.5-9.1) vs 9.3 (IQR 9.0-9.5) mg/dl; median 1.16 (IQR 1.1-1.2) vs 1.23 (IQR 1.21-1.27) mmol/L] ($p<0.01$), magnesium [median 1.9 (IQR 1.8-2.0) vs 2 (IQR 1.9-2.1) mg/dl - $p<0.01$] and PTH [median 10 (IQR 8-13) vs 29 (IQR 22-35) pg/ml - $p<0.01$] were significantly lower in Group A vs Group B. Conversely, serum phosphate [median 3.7 (IQR 3.4-4.1) vs 3.3 (IQR 3.0-3.6) mg/dl - $p<0.01$], calcium-phosphate product [median 33 (IQR 30-36) vs 30 (IQR 27-34) - $p=0.012$] and 25-OH vitamin D [median 34.1 (IQR 29.2-41.3) vs 26.7 (IQR 18.1-33.4) - $p<0.01$) were significantly higher in Group A vs Group B. Twenty-four hour urinary calcium was higher in group A [median 248 mg (IQR 166-363)] than in group B [median 165 mg (IQR 94-229)] ($p<0.01$). The rate of nephrolithiasis was significantly higher in group A (21/60 pts - 35%) than in group B (7/60 pts - 11.7%) ($p<0.01$). Moreover, there was a significant correlation of neprholithiasis with 24h urinary calcium but not with total and ionized serum calcium. Conclusions: This cross-sectional case-control study confirms that treatment of chronic PO-HypoPT with conventional therapy is suboptimal, even in a tertiary referral center, and associated with an increased risk of nephrolithiasis. Following the recent publication of treatment guidelines, the question

of whether a better quality of care, including the use of rhPTH, will improve the biochemical control and decrease the rate of hypercalciuria and the risk of nephrolithiasis remains to be established.

Diabetes Mellitus and Glucose Metabolism

DIABETES COMPLICATIONS II

Improving Screening for Diabetic Retinopathy in a Resident Based Clinic

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Introduction Diabetic retinopathy is the leading cause of blindness in US Adults. In order to improve screening rates, we partnered with the Division of Ophthalmology and installed an onsite retinal camera at our primary care clinic. This led to an improvement in EMR reported screening rates from 20.5% to 44% over the first 3 months. We noticed that any fundus photo, whether gradable or not, led to an automatic annotation in EMR (EPIC) health Maintenance that screening had been completed. Abnormal or ungradable (quality too poor to interpret) retinal photos must be followed up with a complete ophthalmologic evaluation. We designed a chart audit to investigate further whether ungradable retinal photos were being followed up appropriately. **Methods** A retinal camera was installed in the clinic, and patients obtained DR screening during their routine visits from May through October 2018. The nursing staff received training on using the camera and ensuring image quality. These images were then sent to an Ophthalmologist and resulted within the work week. Patients with an abnormal or poor-quality retinal photo were contacted by their resident PCP. We did a retrospective chart review of patients with ungradable photos evaluating whether patients were contacted and whether they followed up with Ophthalmology in the 3 month period after the initial intervention. **Results** Of the 131 patients who received fundus photos in the study period, 29 (22%) had ungradable photos. Twenty-four of these patients were contacted and ophthalmology consults were placed for 22 patients. Eleven (38%) of these patients went on to complete screening with Ophthalmology within 3 months of the ungradable photo. Eighteen patients, or 62% of ungradeable photos, remained incorrectly identified as having completed retinopathy screening by EMR. **Discussion** Over reliance on EMR reporting features can lead to incorrect assumptions about DR screening. Based on this analysis, we need to design better interventions for following up on ungradable photos and ensuring appropriate follow up. One such intervention may be changing how EMR reports ungradable photos. EPIC is a widely used EMR in outpatient settings and other practices may be facing similar issues.

Adrenal

ADRENAL MEDICINE — CLINICAL APPLICATIONS AND NEW THERAPIES

A Multi-Center, Open-Label, Pivotal Phase 2 Study of Azedra® (HSA I-131-MIBG) in Patients with Unresectable, Locally Advanced or Metastatic Pheochromocytoma or Paraganglioma: Updated Long-Term Survival and Safety

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Background: Pheochromocytoma/Paraganglioma (PPGL) are rare neuroendocrine tumors with a 5-yr survival rate as low as 12%. There is a high unmet medical need for effective treatment options for patients with advanced disease. AZEDRA®, a high-specific-activity iodine-131 meta-iodobenzylguanidine (HSA I-131-MIBG), is the first and only FDA-approved therapeutic radiopharmaceutical agent indicated for the treatment of adult and pediatric patients with iobenguane scan positive, unresectable, locally advanced or metastatic PPGL who require systemic anticancer therapy. Methods: Patients with advanced PPGL who were heavily pre-treated and were ineligible for curative surgery or chemotherapy received a dosimetric dose followed by up to two therapeutic doses (each at 296 MBq/kg to a max of 18.5 GBq). The primary endpoint, defined as the proportion of patients with at least 50% reduction of all antihypertensive medication(s) lasting ≥6 months, was met and previously reported. Updated secondary endpoints including overall survival (OS) and safety are reported. Results: A dosimetric dose of HSA I-131-MIBG was administered to 74 patients. Of those, 68 patients received one therapeutic dose and 50 received two doses of HSA I-131-MIBG. Clinical benefit rates (objective tumor responses defined by RECIST 1.0 and stable disease) were observed in 71.4% and 98.0% of patients receiving one and two therapeutic doses, respectively. As of October 10, 2019, median survival time for all patients was 43.2 months (95% CI 31.4, >60). Median survival time was 19.3 months (95% CI 4.5, 32.4) and 49.1 months (95% CI 36.9, >60) in patients receiving one and two doses, respectively. The overall survival was 73.8% at 2 yrs, 47.5% at 4 yrs and 41.5% at 5 yrs. The most common (≥50%) adverse events were nausea, fatigue, and myelosuppression. Myelosuppressive events resolved within 4-8 wks without requiring stem cell transplantation. Late radiation toxicity included 7 patients with secondary malignancies (myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), colon cancer, and lung carcinoma) of which MDS, ALL and AML were considered related to I-131