Thyroid

THYROID CANCER CASE REPORTS I

An Unusual Clear Cell Carcinoma in the Thyroid. Where Is the Primary?

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SUN-480

Background: Clear cell carcinoma in the thyroid gland is rare. It is important to distinguish primary thyroid clear cell carcinoma from metastases, since its clinical behaviors and treatment options were different.

Clinical Case: A 47-year-old woman without past medical history presented to our outpatient surgery department with right neck mass for 8 months. Thyroid ultrasonography revealed a 3.9 cm nodule in the right thyroid. Thyroid function test was within the normal range. Fine needle aspiration cytology of the nodule showed suspicious for neoplasm. She underwent radical total thyroidectomy and lymph node dissection. Pathology revealed an unusual carcinoma comprising cuboidal cells with irregular nuclear contours, some eosinophilic or clear cytoplasm, arranged in infiltrating nests or cords with marked stromal hyalinization, highly suggestive of a clear cell carcinoma. Ectopic thymic tissue was present adjacent to the tumor. By immunohistochemical (IHC) staining, tumor cells were p63 (+), TTF-1 (-), thyroglobulin (-), PAX8 (-), synaptophysin (-), CD5 (-), and CD117 (-). Tumor genetic sequencing detected *EWSR1-CREM* fusion genes. For disease extent evaluation, two out of seven lymph nodes obtained during operation were positive of tumor metastases. Whole body computed tomography (CT) 3 months after operation revealed no residual thyroid tissue, neck lymphadenopathies or intra-abdominal metastases. A pulmonary ground-glass opacities of 7mm in diameter was found, which was stationary at a repeated CT scan 6 months later.

Clinical Lesson: Clear cell carcinoma in the thyroid gland could be primary, arising from clear cell change of follicular or papillary thyroid carcinoma. The negative IHC stain of thyroglobulin, TTF, PAX8, as well as lack of papillary or follicular architecture made primary thyroid clear cell carcinoma unlikely. Most of the metastatic clear cell carcinoma to the thyroid gland arose from renal primary. However, there was no clinical or radiographic evidence of renal tumor in our case. Although ectopic thymic tissue was identified on pathology, negative IHC staining of PAX8, CD5 and CD117 made thymic origin less likely. Positive IHC staining of p63 and a novel *EWSR1-CREM* fusion gene confirmed the diagnosis of salivary clear cell carcinoma. According to our literature review, there were only 3 cases of clear-cell carcinoma with *EWSR1-CREM* fusion gene (1), and our case is the first case who presented with clear cell carcinoma in the thyroid. In conclusion, the importance of IHC stain and molecular testing in determining the primary origin of clear cell carcinoma were addressed in our case.

Reference: (1) Chapman E, et al. *Am J Surg Pathol.* 2018;42(9):1182-1189

Adrenal

ADRENAL - CORTISOL EXCESS AND DEFICIENCIES

Association Between Long-Term Prednisolone Induced Adrenal Insufficiency and Polymorphisms in the Glucocorticoid Receptor Gene

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OBJECTIVE: Several biomarkers for glucocorticoid (GC) sensitivity have been proposed relevant for the inter-individual variation seen in treatment response and side effects to GC treatment. Four single nucleotide polymorphisms (SNPs) of the GC receptor (GR) gene have been associated with increased (*Bcl*1 and N363S) or decreased (9β and ER23/23EK) GC sensitivity. We investigated the influence of these proposed biomarkers for GC sensitivity on GC-induced adrenal insufficiency.

SUBJECTS AND METHODS: We included 239 patients receiving long-term prednisolone treatment for rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) / giant cell arteritis (GCA), or after renal transplantation (RTx). Four GR gene SNPs (*Bcl*1 rs41423247; 9β rs6198; N363S rs56149945; ER22/23EK rs6189 + rs6190) were sequenced by Sanger sequencing. Adrenal function was evaluated by a 250 µg corticotropin stimulation test. To compare allele frequencies with background population, two control groups were generated from two regional whole-genome databases. We downscaled each genome dataset to 239 individuals/group to balance statistical analysis.

RESULTS: In total 239 patients were genotyped and 178 of these (RA n=103, PMR/GCA n=47, RTx n=28) treated with a median current dose of 5 mg prednisolone/day (interquartile range 5-7 mg) and a median treatment duration of 48 months (interquartile range 22-111 months) completed

the corticotropin test. Seventy-three (41%, CI95%: 34-48%) patients had an insufficient response to the corticotropin test. Neither the risk of adrenal insufficiency, unstimulated nor stimulated P-cortisol levels were directly associated with any of the GR SNPs. However, for both insensitive SNPs 9β and ER23/23EK the effect of current prednisolone dose on stimulated P-cortisol was smaller (higher dose did not suppress the cortisol level as much) in carriers vs. non-carriers (p=0.035 and p=0.0075). The same sensitivity-associated tendency was seen for the N363S, but not the *Bcl*1 SNP. The *Bcl*1 SNP occurred more frequently in our cohort compared with control groups (63% vs. 40%, p<0.0001). The same trend was seen for the other sensitive but less frequent SNP N363S. The 9β SNP also occurred more frequently in our cohort (18% vs. 13%, p=0.029), but depending on regional sub cohorts in one control group.
CONCLUSION: The GR SNPs did not directly associate to the risk of adrenal insufficiency, unstimulated nor stimulated cortisol levels, respectively. However, the effect of prednisolone dose on stimulated cortisol depended on the GR SNPs: Cortisol was less suppressed with higher current prednisolone dose in patients carrying the insensitive SNPs. The substantially higher frequency of the *Bcl*1 SNP is remarkable even with modest n=239. It questions whether there is an association between carrying the sensitive GR SNPs and inability to taper GC treatment ending up in this cohort of long-term treated patients.

Pediatric Endocrinology

PEDIATRIC OBESITY, THYROID, AND CANCER

Risk of Long-Term Endocrine Sequelae in Survivors of Progressing Childhood Optic Pathway Glioma Treated by Upfront Chemotherapy: Preliminary Analyses of 102 Subjects from the French Multicentric BB-SFOP Registry

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For the brain tumor committee of SFCE (Societe´ Française des Cancers de l'Enfant). Objective: Therapeutic approach favors chemotherapy as the first-line-treatment in progressing OPG. There are few data on long term endocrine outcomes of aggressive OPG treated by upfront chemotherapy. Our main objective was to describe the long-term endocrine sequelae in these patients and to identify potential early predictors of the endocrine involvement. Subjects and methods: Children diagnosed with OPG at an age younger than 16 years from the French multicentric BBSFOP registry were included. They were treated with upfront chemotherapy according to the BB-SFOP protocol in France between June 1990 and December 2004, and subsequent treatment (second-line chemotherapy, surgery, radiotherapy) was used depending on tumor progression. They underwent a late evaluation with clinical and biological assessment between January 2011 and March 2016. Results: One hundred and two patients were included in our study. The mean age at tumor diagnosis was 3.3±0.3 years. The mean time of follow-up was 13.9±3.7 years. A history of precocious puberty was present in 36% of the subjects. At least one endocrine deficiency was present in 93% of the subjects (GHD 74%, TSH deficiency 57%, ACTH deficiency 36%, hypogonadotropism 33%, gonadic deficiency 30%, diabetes insipidus 15%; inappropriate AVP secretion 7%). 37% of males and 39% of females were overweight or obese. Mean adult height, reached in 51 subjects, was -1.2±1.3 SDS in males, and -0.7±1.4 SDS in females. Chemotherapy only was protective from pituitary deficiencies (odds ratio 0.19 to 0.37, $P < 0.05$). NF1 was protective from TSH and ACTH deficiencies (odds ratio 0.25 to 0.35, $P < 0.05$). Tumor volume on diagnostic MRI was not predictive of pituitary deficiencies. Gonadic deficiency was significantly more frequent in males than females (46,5% vs 12.2%, $P < 0.05$), and associated with chemotherapy only (OR 3.2, $P < 0.05$) and NF1 (OR 4.8, $P < 0.05$). Overweight/Obesity was associated with ACTH deficiency (OR 5, $P < 0.05$).Conclusion: Obesity and late endocrine dysfunction were frequent in subjects treated by upfront chemotherapy for aggressive OPG during childhood. However, chemotherapy only, when possible, was protective from pituitary involvement.

Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY

Systematic Screening Reveals Large Number of Undiagnosed and Untreated Cardiovascular Risk Factors in Adults with Prader-Willi Syndrome

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MON-284

Introduction: Prader-Willi syndrome (PWS) is a complex hypothalamic disorder, combining hypotonia, intellectual disability (ID), pituitary hormone deficiencies and hyperphagia. In PWS, up to 3% of patients die every year. In half of the patients, the cause of death is obesity related and / or of cardiovascular (CV) origin.
Obesity is caused by hyperphagia combined with a low energy expenditure. Untreated hormone deficiencies like hypogonadism and hypothyroidism can cause low muscle mass and low basal rest metabolism (BRM) leading to this low energy expenditure. Patients with PWS should exercise one hour daily to compensate for their low BRM. However, hormone deficiencies usually cause fatigue, leading to exercise intolerance. Musculoskeletal and / or behavioral problems can also cause reduced physical activity. The subsequent sedentary lifestyle can induce CV risk factors like hypertension, hypercholesterolemia and diabetes mellitus (DM).
Another risk factor often present in PWS is sleep apnea, which can be central (CSA), obstructive (OSA) or both. Both CSA and OSA can lead to pulmonary hypertension and a further increase in obesity.
The above mentioned health problems often remain unnoticed and untreated, which is partly due to the behavioral phenotype of PWS (patients seldomly report pain and hardly ever complain about physical problems). However, if left untreated, these risk factors can cause CV complications leading to hospital admission or even death. To reveal yet