Thyroid

THYROID NEOPLASIA AND CANCER

Diffuse Sclerosing Variant Papillary Thyroid Cancer: Clinical and Histopathological Features, Mutational Profile, Management and Outcome

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MON-533

Diffuse sclerosing variant (DSV) is a rare subtype of papillary thyroid cancer (PTC). Whether it represents a higher grade subtype than conventional PTC is not quite clear. Furthermore, there are limited data on its long-term outcome and its molecular genetics. In this report, we studied all cases of DSV PTC seen at our center during the last 20 years. Out of more than 6000 patients (pts) with differentiated thyroid cancer, only 37 were DSV. We reviewed the clinical and histopathological features, management and outcome of these cases. In addition, molecular genetics is partially achieved; 17 out of these 37 cases have been genotyped for $BRAF^{V600E}$, *TERT* promotor mutations, *NRAS, HRAS and KRAS* mutations. The molecular profiling of the other 20 cases is being done. A total of 37 pts were studied {(12 Males:25 Females, median age 21 years (8-89)}. One pt had lobectomy and the other 36 pts (97.3%) had a total thyroidectomy. Central only (4 pts) or central/lateral lymph node dissection (29 pts) were performed. The median tumor size was 4.5 cm (1.5-8.1). The tumor was multifocal in 27 cases (73%), with extrathyroidal invasion in 27 (73%) and lymphovascular invasion in 24 pts (64.8%). A background lymphocytic thyroiditis was present in 12 pts (32.4%). Lymph node metastases were present in 34 pts (92%) and distant metastases in 13 pts (35%). The sites of metastasis are lungs in 12 pts (32.4%) and lungs and bone in 1 pt. Twenty pts (54.1%) were in TNM8 stage 1, 10 pts (27%) in stage 2, 1 (2.7%) in stage 4a, 3 (8.1%) in stage 4b and 3 unstageable. The ATA risk classification for these pts was 4 pts (10.8%) in low, 12 (32.4%) in intermediate, 19 (51.4%) in high-risk groups and 2 could not be assessed. I-131 was administered to 33 pts (89.2%). The median administered activity was 136 mCi (46-218). Fifteen pts (40.5%) received additional therapies (3 surgeries, 7 RAI, 5 surgeries, and RAI). In 17 pts (46%) which were genotyped, only 3 tumors (8.1%) had $BRAF^{V600E}$ mutation, 1 (2.7%) had *TERT* promotor C228T mutation and none had *RAS* mutations. At the last follow up, 15 pts (40.5%) achieved an excellent response, 9 (24%) an indeterminate response, 6 (16.2%) with a structural disease, and 7 (19%) were lost for follow up.

Conclusion: DSV PTC is a rare variant, occurs mostly in adolescent and young pts, characterized by aggressive histopathological features and high rates of lymph node and distant metastases but the commonly reported mutations in PTC are rare in DSV and mortality is absent.

Diabetes Mellitus and Glucose Metabolism

CLINICAL STUDIES IN OBESITY, DIABETES RISK, AND CARDIOVASCULAR OUTCOMES

Heterogeneity of Familial Partial Lipodystrophy Type 2 from a Genotype-Phenotype Perspective.

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SAT-622

Phenotypic heterogeneity is a well-known feature of Familial Partial Lipodystrophy Type 2 (FPLD2) which is caused by pathogenic variants in the *LMNA* gene. Clinical diagnosis can be challenging in some cases. Likewise, trained physicians can report differences in body composition and clinical manifestation of FPLD2, highlighting the importance of accurate phenotyping. In this study, we aimed to identify phenotype-genotype correlations in a cohort of systematically evaluated patients with FPLD2. We retrospectively evaluated 43 patients diagnosed with FPLD2 (age 50.3±16.1 years, 79.1% women). Per pathogenic variants, patients were divided into two groups; 24 with R482Q (RQ: 55 ± 3.2 years, 70.8% women) and 19 with non-R482Q (Non-RQ: 46 ± 3.2 years, 84.2% women). Non-RQ group consisted of several pathogenic *LMNA* variants in exons 1, and 5 through 11. Also, DEXA parameters were studied in a subgroup of 19 patients with available assessments (in 11 RQ and 8 non-RQ patients) that were matched for age, sex and BMI. Patients in the RQ group were older when they were first diagnosed with lipodystrophy (48.6 ± 3.2 years and 37.4 ± 3.1 years, $p = 0.03$). Although the prevalence of diabetes, hepatic steatosis and other co-morbidities associated with metabolic control were similar in both groups at the time of the study, patients with RQ pathogenic variants were diagnosed later in life with diabetes (46.0 ± 4.2 years vs. 35 ± 3.5 years, $p = 0.03$) and hepatic steatosis (45.3 ± 6.9 years vs. 30.1 ± 3.7 years, $p < 0.01$. Although more pancreatitis episodes were reported in the RQ group (13 ± 3 vs. 2 ± 1, $p = 0.02$), the number of patients with a history of pancreatitis was similar across the groups suggesting the occurrence of recurrent pancreatitis episodes in selected patients with RQ pathogenic variant. Pain was a common complaint among the patients, but it was less severe in the RQ group (4.2±2.1 vs 2.3±2.0, p=0.05). In terms of body composition, patients with RQ pathogenic variants had greater bone mass (legs: 879 ± 59.3 g vs. 703.5 ± 33.7 g, p= 0.01; trunk 914.2 ± 65.5 g vs. 674.1 ± 28.0 g, $p = 0.005$, total body: 2643.7 ± 158.9 g vs. 2140.6 ± 78.4 g, $p = 0.005$) and higher fat mass in the legs (19 vs. 14%, $p = 0.02$). Similarly, patients with RQ pathogenic variants had less lean percentage (76 vs. 81%, $p = 0.009$), and accordingly, less fat-free mass percentage (80 vs. 85%, $p = 0.02$) in the legs. Total fat-free mass of the RQ group was also lower (66 vs. 76%, $p = 0.0009$). Genotype-phenotype characterization is important not only for understanding the natural history and clinical manifestation of the disease but also for establishing more accurate and precise diagnostic

criteria or therapeutic approaches. Our data suggest more fat preservation in *LMNA* R482Q carriers, presumably leading to a later diagnosis of lipodystrophy and metabolic abnormalities. More studies are needed to confirm the differences observed in body composition.

Adrenal

ADRENAL - HYPERTENSION

Effectiveness of Pre-Op α-Blockade on Intra-Op Blood Pressure Control in Patients with Pheochromocytoma

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MON-205

Abstract:
Pheochromocytoma are rare tumors arising from catecholamine producing chromaffin tissue. Surgical manipulation of pheochromocytoma inevitably leads to supraphysiologic levels of circulating catecholamines. Such manipulation has the potential to lead to an intra-operative hypertensive crisis, cardiac arrhythmia, myocardial infarction, or pulmonary edema. When inadequately primed pre-operatively, a patient exposed to such surges may experience life-threatening consequences.
Phenoxybenzamine is a non-competitive, non-selective α_1 and α_2 receptor antagonist that prevents blood pressure liability during surgical resection of pheochromocytoma. Previous literature has suggested that phenoxybenzamine affords more pronounced peri-operative systolic blood pressure control as compared to selective alpha-blockers. This superior control potentially is at the cost of postoperative hypotension owing to the irreversible nature of phenoxybenzamine. [1]
Our study compares the effects of pre-operative phenoxybenzamine on perioperative outcomes at a single tertiary medical center from 2004 to 2019. The cumulative pre-operative phenoxybenzamine dose was compared to the maximum intra-operative blood pressure, need for IV blood pressure lowering medications, duration of vasopressor need, volume replacement need, duration of time in the OR, duration of hospital stay, and pre-operative catecholamine levels. We speculate that increased phenoxybenzamine exposure will result in reduced peak intra-operative blood pressure and need for IV blood pressure lowering medications but may increase the need for post-resection intra-operative vasopressors and post-resection volume replacement.
After IRB approval, (ID #00031606), we performed a data warehouse query for the ICD 9 and 10 codes of "pheochromocytoma" and "paraganglioma". Patients who did not have confirmed pheochromocytoma on pathology were excluded. Data was collected retrospectively on 30 patients who underwent adrenalectomy for pheochromocytoma. 14 charts were excluded due to incomplete intra-operative anesthetic documentation.
Our results suggest that there is no significant correlation between peak intra-operative MAP and cumulative phenoxybenzamine exposure. The cumulative dose of pre-operative phenoxybenzamine did not correlate with the number of anti-hypertensive medications used intra-operatively. An increased cumulative dose of pre-operative phenoxybenzamine was not associated with an increased duration of intra-operative vasopressor medications. Intra-operative volume replacement needs were surprisingly reduced with increased cumulative pre-operative phenoxybenzamine exposure.

[1] P.A. van der Zee, A. de Boer. Pheochromocytoma: A review on preoperative treatment with phenoxybenzamine or doxazosin. *The Netherlands Journal of Medicine*. May 2014; Vol. 72 No 4, 190-201.

Tumor Biology

TUMOR BIOLOGY: GENERAL, TUMORIGENESIS, PROGRESSION, AND METASTASIS

An Affair of the Heart - First Case Report of Immune Checkpoint Inhibitor Associated Cardiac Sarcoidosis Presenting with Non-PTH Medicated Hypercalcemia

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SAT-116

Background:
Immune checkpoint inhibitors (ICI) are an effective new tool in the treatment of malignancy by rescuing exhausted T-cells and enhancing anti-tumor immunity. The offset of immune self-tolerance can result in autoimmune adverse effects involving gastrointestinal, pulmonary and endocrine systems. Lung and skin sarcoidosis have been described in association with ICI use. We present the first case of non-PTH medicated hypercalcemia due to cardiac sarcoidosis in the setting of immunotherapy.
Case Presentation:
A 71-year-old man was referred to endocrinology for hypercalcemia. He had a fourteen-year history of scalp melanoma in remission until February 2019, when routine surveillance scans suggested metastatic disease. Computer tomography of the chest showed mediastinal and hilar lymphadenopathy (largest node 5.2 cm) and numerous pulmonary nodules (largest 1.7 cm). Biopsy of the largest pulmonary nodule and mediastinal lymph node (LN) confirmed BRAF wild-type metastatic melanoma. Ipilimumab/nivolumab (antiCTLA4/antiPD-1) combination therapy was started. After two cycles, hypercalcemia was noted on routine laboratory surveillance. He was asymptomatic and physical exam was unremarkable. Initial workup revealed: calcium 10.6 mg/dL (8.6-10.2), albumin 4 g/dL (3.5 - 5.2), phosphorus 3.8 mg/dL (2.7 - 4.5), PTH <0.6 pg/mL (15.0 - 65.0), PTHrP <2.0 pmol/L (0.0 - 2.3), 25 hydroxyvitamin D 22. 9 ng/mL (30 - 60), vitamin A 0.59 mg/L (0.30 - 1.20). He denied taking calcium-containing supplements. He was treated with hydration and immunotherapy was continued for two cycles, followed by single agent nivolumab. After three months on ICI, the metastatic lesions were reduced in size by 30%. His calcium peaked at 12.5 mg/dL and was treated with 4mg of intravenous Zoledronic acid without resolution. He developed worsening functional status, symptomatic hypotension, and elevated troponins. Cardiac MRI demonstrated myocarditis and nivolumab-induced myocarditis was suspected. Surprisingly, endomyocardial biopsy revealed multiple granulomas suggestive of sarcoidosis. AFB, PAS and Congo red stains were negative. He