Thyroid

THYROID NEOPLASIA AND CANCER

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

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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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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