



Correlation between Pro-inflammatory biomarkers and papillary thyroid cancer: A case control Study

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Abstract

Introduction: Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. Apart from genetics, autoimmunity has been implicated in its pathogenesis. In this context, we set out to study the role of Pro-inflammatory cytokines in PTC in South Indian population.

Material and methods: This pilot prospective case-control study was conducted on surgically managed PTC patients. Institutional ethical committee approval was obtained. Diagnosis of PTC was based on imaging, fine needle aspiration cytology and later confirmed by histopathology. Exclusion criteria were subjects with any disease or medication interfering with the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 46 PTC subjects and 44 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF- α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.

Results: The mean hsCRP level in PTC and controls were 18.3 ± 3.1 mg/mL and 5.5 ± 1.2 mg/mL respectively. The mean TNF- α level, IL-6 level and Leptin levels were 295 ± 28 pg/mL, 13.6 ± 4.4 pg/mL and 1.93 ± 0.8 ng/mL respectively. Serum leptin level in controls was 3.6 ± 1.8 ng/mL. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value <0.05) with negative correlation for leptin levels.

Conclusions: Our study shows raised titers of pro-inflammatory markers – IL-6, TNF- α and hsCRP, while reduced leptin levels correlated with PTC suggesting a contributory role. But, the exact immuno-modulatory mechanism needs more research.

Keywords: Papillary thyroid cancer; Tumour necrosis factor; Interleukin-6; Goiter; Auto-immunity; Leptin

Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. Apart from the role of genetics, autoimmunity has been implicated in its etiopathogenesis and prognostication. Autoimmunity is an important arm of immune pathophysiology. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF- α), high sensitive C reactive protein (hsCRP) and leptin levels are commonly measured markers in autoimmune conditions. In this context, we set out to study the role of Pro-inflammatory biomarkers in PTC in Indian population.

Material and methods

This pilot prospective case-control study was conducted on surgically managed PTC patients. Institutional ethical committee approval was obtained. Diagnosis of PTC was based on imaging, fine needle aspiration cytology and later confirmed by histopathology.

Exclusion criteria were subjects with any systemic or chronic inflammatory disease or any medication, which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Other variants of thyroid cancer (follicular, medullary, anaplastic, lymphoma) were also excluded. Serum samples were collected from 46 PTC subjects and 44 age matched healthy controls. Pro-inflammatory biomarkers (PIM) – Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF- α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.

Results

All the cases of PTC underwent total thyroidectomy with additional neck dissection in 27% of PTC cases. All the surgical thyroidectomies were uneventful with no mortality, permanent recurrent laryngeal nerve palsy or permanent hypoparathyroidism.

The mean hsCRP level in PTC and controls were 18.3 ± 3.1 mg/mL and 5.5 ± 1.2 mg/mL respectively. The mean TNF- α level, IL-6 level and Leptin levels were 295 ± 28 pg/mL, 13.6 ± 4.5 pg/mL and 1.93 ± 0.7 ng/mL respectively. The comparative PIM profile is shown in Chart 1. Serum leptin level in controls was 3.6 ± 1.8 ng/mL. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value <0.05) with negative correlation for leptin levels. A PTC subset analysis of PIM profile between those with and without HT component showed statistically non-significant correlation.

Discussion

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. Apart from the role of genetics, autoimmunity has been implicated in its etiopathogenesis. The role of local thyroid autoimmunity was hypothesized, as several pathological studies showed significant association of Hashimoto's thyroiditis (HT) within the gland with PTC. The incidence and association between HT and PTC is reported variably in literature (1,2). HT-associated malignancy as a surgical indication has been addressed in many studies (3-5), but end up concluding that malignancy is largely coincidental with no causative correlation between HT and PTC. The prognostic influence of HT on PTC is also an enigma. Few studies reported better prognosis, better cure rate and lower stage PTC, when associated with HT (6). Some of the reports show no prognostic influence of HT on outcomes in PTC (7). On the contrary, studies also reported poorer prognosis, more chances of recurrence and aggressive PTC, when associated with HT (8). Thus, the reports have been conflicting ranging from causative, protective and neutral role of immunomodulation.

The serum pro-inflammatory biomarkers offers an objective, repeatable and evaluable option to measure the autoimmune activity. Several studies shows raised titres of cytokines, blood markers and circulating miRNAs in PTC (9-12). Obesity related leptin level showed significant correlation in PTC (13). Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF- α), high sensitive C reactive protein (hsCRP) and leptin levels are commonly measured markers in autoimmune conditions. To address the role of PIM in PTC, we contemplated this study. As shown in the results, the PIM titres showed statistically significant increase in PTC compared to controls. But, subset analysis of PIM profile in

PTC with and without HT component, showed a non-significant correlation, suggesting that HT had a neutral influence on the serum PIM profile. Probably, the PTC stimulated release of PIMs by an unknown autoimmune inflammatory mechanism, independent of HT. We speculate this preceding hypothesis as the controls showed lower PIM titers compared to PTC cases. But, we have not evaluated the prognostic influence of PIMs on PTC, as this objective was beyond the scope this paper. Further, analysis of PIM in PTC subtypes are not evaluated in this study, as the primary focus was to study correlation of PIMS between PTC cases and controls.

The positive outcomes of this study are preoperative serum PIM in PTC, correlation of the PIM titers between PTC cases and controls, analysis in histopathologically confirmed tissues rather than cytology specimen and first of its kind study from India. The apparent drawback of our study is smaller cohort size, non-randomization and non-specificity of these PIM profile. We need larger studies (preferably prospective randomized controlled trials) from multiple centers from different geographical areas to establish and routinely utilize our findings. Though, the confirmation of role of autoimmunity in PTC is sub-optimal through this study, our data provisionally hints at significant correlational pattern between these serum PIMs and PTC in comparison with controls. If the authenticated in future, these serum PIMs in PTC, might help in better inter-institutional comparison of data, auditing and prognostication. Clear prognostic grading, based on this pro-inflammatory biomarker profile can also lead to optimal management and follow-up protocols.

Conclusions

Our study shows raised titers of pro-inflammatory markers – IL-6, TNF- α and hsCRP, while reduced leptin levels correlated with PTC suggesting a contributory role. But, the exact immuno-modulatory role and pathogenetic mechanism in PTC needs more research. PIM profile could serve as potential surrogate marker of autoimmune pathophysiology in PTC.

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