

Concurrent Presence of Hashimoto's Thyroiditis with Papillary Carcinoma of Thyroid- A Retrospective Study

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ABSTRACT

Introduction: Hashimoto's thyroiditis is the most common inflammatory disease of thyroid. Papillary carcinoma of thyroid is an epithelial malignancy and is the most frequent thyroid neoplasm. The association between Hashimoto's thyroiditis and papillary carcinoma of thyroid has been debatable due to conflicting evidence.

Aim: To know the socio-demographic determinants of Hashimoto's thyroiditis and to find out the association between Hashimoto's thyroiditis and papillary carcinoma of thyroid.

Materials and Methods: In this retrospective study, clinical and histopathological data of 720 patients who underwent thyroidectomy between October 2013 to September 2018 were studied at Father Muller Medical College, Mangalore, Karnataka, India. Clinical case records, from October 2013 till September 2018, and histopathological reports were collected. The results were expressed in percentages, proportions and means with standard deviation. Chi-square test was used to find out the association of age group, sex and histopathologic findings with

Hashimoto's thyroiditis. The data was analysed using Statistical Package for the Social Sciences (SPSS) version 23.0 and p-value <0.05 was considered as statistically significant.

Results: Mean age of the study participants with and without Hashimoto's thyroiditis was 45.94 (± 10.60) years and 45.88 (± 12.88) years respectively. Out of 720 study participants, 623 (86.5%) were females and 97 (13.5%) males. The most common indication for thyroidectomy was benign thyroid disorders followed by papillary carcinoma of thyroid. Hashimoto's thyroiditis was seen significantly higher in females compared to males ($\chi^2=12.214$, $p<0.001$) and odds of females having Hashimoto's thyroiditis was 3.76 times that of males. Papillary carcinoma was seen in 157 cases out of 720 cases, and amongst them, 51 (32.5%) had Hashimoto's thyroiditis. Papillary carcinoma was found to be associated with the presence of Hashimoto's thyroiditis ($\chi^2=17.5$, $p<0.001$).

Conclusion: Female sex was the significant socio-demographic determinant of Hashimoto's thyroiditis. Papillary carcinoma of thyroid was found to be associated with Hashimoto's thyroiditis.

Keywords: Carcinoma, Lymphocytic thyroiditis, Socio-demographic, Thyroidectomy

INTRODUCTION

Papillary thyroid carcinoma is the most common amongst the malignant cancers of thyroid comprising 70-80% of all thyroid cancers [1]. Chronic lymphocytic thyroiditis is the most prevalent autoimmune endocrine disorder in females [2]. Usually, the well-differentiated carcinoma and chronic lymphocytic thyroiditis remain asymptomatic for a long time and are usually found to be incidentally diagnosed on histological examination of thyroidectomy specimens [1]. In the meta-analysis by Singh B et al., papillary carcinoma of thyroid was found to be associated with Hashimoto's thyroiditis almost three times more frequently than other types of thyroiditis [3]. The concurrent presence of Hashimoto's thyroiditis and papillary carcinoma of thyroid is reported between 10-58% [4,5]. Few studies did not find any significant association between Hashimoto's thyroiditis and papillary carcinoma of thyroid [6-8].

Chronic inflammation is considered as a risk factor for the development of certain malignant tumours. Lymphocytic infiltration is frequently observed in differentiated thyroid carcinoma, suggesting the role of immunological factors in tumour progression [9,10]. However, the causal association is yet to be proven. Early identification of Hashimoto's thyroiditis may be helpful for clinicians in predicting the papillary carcinoma of thyroid and preventing its progression.

The present study was done to find out the association of socio-demographic variables and malignancies especially papillary carcinoma of thyroid with Hashimoto's thyroiditis.

MATERIALS AND METHODS

This was a retrospective study that included patient data from October 2013 till September 2018 and the analysis of the data was

done in September 2018. Ethical clearance was obtained vide no. FMMCI/CCM/28/2019 from the Institution Ethics Committee of Father Muller Medical College, Mangalore, Karnataka, India. Waiver of consent was taken from the Ethics Committee as the data was extracted from the clinical case records. The patients' data was kept completely confidential and the personal identifiers were never revealed in any form while entering or reporting the results.

Inclusion criteria: The records of all the patients who underwent thyroidectomy during the five years duration were reviewed. These were made available from the Inpatient Medical Records Department of the Institution.

Exclusion criteria: Patients who underwent thyroidectomy due to trauma/medicolegal reasons were excluded from the study.

Socio-demographic (age and sex) and clinical data of all the 720 patients who underwent thyroidectomy (total, completion, near total, hemi, subtotal) during the five years duration were analysed. Data was extracted from the clinical case records and histopathological reports of all the patients, by a predesigned validated observation checklist.

Diagnosis of Hashimoto's thyroiditis and papillary carcinoma of thyroid was based on histopathological findings. The common histopathologic findings in Hashimoto's thyroiditis were extensive lymphocytic infiltrate with germinal center formation, atrophic follicles with abundant hurthle cells, oxyphilic metaplasia of follicular cells and nodularity [11]. The histopathological findings in papillary carcinoma of thyroid were based on nuclear features and cell variants.

STATISTICAL ANALYSIS

The results were expressed in percentages, proportions and means with standard deviation. Chi-square test was used to find out the

association of age group, sex and histopathologic findings with Hashimoto's thyroiditis. The data was analysed using Statistical Package of Social Sciences (SPSS) version 23.0 and p-value <0.05 was considered statistically significant.

RESULTS

A total of 720 patients underwent thyroidectomy in the institution during the study period. It was found that 344 (47.8%) patients underwent total thyroidectomy, 310 (43.1%) patients near total thyroidectomy, 22 (3.1%) completion thyroidectomy, 8 (1.1%) patients subtotal and 36 (5%) hemithyroidectomy, respectively.

The most common reasons for thyroidectomy were benign thyroid disease and papillary carcinoma of thyroid [Table/Fig-1]. All the patients with papillary carcinoma of thyroid 157 (21.8%) underwent total thyroidectomy. Amongst them, only 14 patients underwent modified radical neck dissection, 30 central compartment neck dissection and 11 selective neck dissection respectively.

Indications	Frequency (%) (N=720)
Hashimoto's Thyroiditis (HT)	42 (5.8%)
Benign thyroid disease	430 (59.7%)
Papillary carcinoma	106 (14.7%)
Papillary carcinoma with HT	51 (7.1%)
Medullary carcinoma	7 (1%)
Anaplastic	2 (0.3%)
Follicular carcinoma	25 (3.5%)
Benign thyroid disease with HT	51 (7.1%)
Medullary with HT	1 (0.1%)
Follicular carcinoma with HT	3 (0.4%)
SCC infiltrating	1 (0.1%)
Parathyroid neoplasm	1 (0.1%)

[Table/Fig-1]: Indications for thyroidectomy.

Out of 148 cases of thyroiditis, the majority of them were patients above the age of 45 years, though there was no association between the age of the patient and the presence of Hashimoto's thyroiditis. The odds of females having Hashimoto's thyroiditis was 3.76 times that of males and this was found to be statistically significant ($\chi^2=12.214$, $p<0.001$, df 1). Hashimoto's thyroiditis was most commonly seen with papillary carcinoma of thyroid or benign thyroid disease. A total of 195 specimens showed malignancy on histopathological evaluation and the most common malignancy observed was papillary carcinoma of thyroid in 157 cases [Table/Fig-2].

The multiple strata of [Table/Fig-2] for histopathology findings were reduced to only two i.e., presence or absence of papillary carcinoma to see any association of papillary carcinoma of thyroid with Hashimoto's thyroiditis [Table/Fig-3].

Of the 157 papillary carcinoma cases, 51 (32.5%) had Hashimoto's thyroiditis, compared with 97 (17.2%) out of 563 cases with other pathologies. Patients who had papillary carcinoma were more than 2.31 times likely to have Hashimoto's thyroiditis than the patients who did not have papillary carcinoma. Papillary carcinoma was found to be associated with the presence of Hashimoto's thyroiditis ($\chi^2=17.5$, $p<0.001$, df 1) [Table/Fig-3].

DISCUSSION

Hashimoto's thyroiditis is associated with varying degrees of thyroid hypofunction [12]. It is estimated to have an incidence of about 0.3-1.5 cases per 1000 persons [13]. The incidence is 10-15 times higher in females. Within diffuse Hashimoto's thyroiditis, benign and malignant nodules could also co-exist [14]. Few thyroid malignancies are associated with Hashimoto's thyroiditis such as thyroid lymphomas and papillary carcinoma of thyroid [15,16]. Hence, in

Hashimoto's thyroiditis		Present (n=148)	Absent (n=572)	χ^2 , p-value	Odds ratio
Mean age \pm SD (in years)		45.94 \pm 10.60	45.88 \pm 12.88		
Age group (in years)	\leq 45	67 (18.9%)	287 (81.1%)	1.132, 0.287	>45/ \leq 45=1.218
	>45	81 (22.1%)	285 (77.9%)		
Sex	Male	7 (7.2%)	90 (92.8%)	12.214, <0.001	Female/male=3.759
	Female	141 (22.6%)	482 (77.4%)		
Histopathology findings	Benign thyroid disease	51 (10.6%)	430 (89.4%)	NA	
	Papillary carcinoma	51 (32.5%)	106 (67.5%)		
	Medullary carcinoma	1 (12.5%)	7 (87.5%)		
	Anaplastic carcinoma	0	2 (100%)		
	Follicular carcinoma	3 (10.7%)	25 (89.3%)		
	Hurthle cell carcinoma	0	0		
	SCC infiltrating	0	1 (100%)		
	Parathyroid neoplasm	0	1 (100%)		
	Hashimoto's thyroiditis	42 (100%)	0		

[Table/Fig-2]: Distribution of Hashimoto's thyroiditis by age, sex and histopathologic findings. p-value <0.05 was considered statistically significant

Papillary carcinoma	Hashimoto's thyroiditis		χ^2 , p-value	Odds ratio
	Present (n=148)	Absent (n=572)		
Present	51 (32.5%)	106 (67.5%)	17.5, <0.001	2.231
Absent	97 (17.2%)	466 (82.8%)		

[Table/Fig-3]: Association between Hashimoto's thyroiditis and papillary carcinoma of thyroid. p-value <0.05 was considered statistically significant.

the present study, the socio-demographic and histopathologic determinants of Hashimoto's thyroiditis were explored.

The most common indication of thyroidectomy in the study was benign thyroid disease with or without Hashimoto's thyroiditis (66.8%), followed by papillary carcinoma of thyroid with or without Hashimoto's thyroiditis (21.8%), Hashimoto's thyroiditis (5.8%), and other forms of carcinoma [Table/Fig-1]. The papillary carcinoma of thyroid was observed to be the most common malignancy.

Hashimoto's thyroiditis is a form of chronic lymphocytic thyroiditis of autoimmune aetiology found more commonly in females. In the present study also, out of 148 Hashimoto's thyroiditis patients, 95.3% were females. Similar results were observed by Repplinger D et al., where 90% of the patients with Hashimoto's were females [17]. Konturek A et al., Mazokopakis E et al., Liu X et al., also observed a higher prevalence of Hashimoto's in females [6,7,18]. In contrast, Singh B et al., did not observe any association of female sex with Hashimoto's thyroiditis [3].

Hashimoto's Thyroiditis is the most common inflammatory thyroid disease. It is speculated that Hashimoto's thyroiditis may be a possible risk factor for papillary carcinoma of thyroid and might be having a causative relationship with it [19]. Malignant transformation in the thyroid gland could be either due to cellular mediators produced by chronic inflammatory cells or by higher blood levels of thyroid stimulation hormone which stimulates follicular epithelial proliferation [20]. In this study, 32.5% of papillary carcinoma of thyroid cases had association with Hashimoto's thyroiditis. According to the other studies, the association between papillary carcinoma of thyroid and chronic lymphocytic thyroiditis has been reported less. Mathews R et al., had observed 16% of papillary carcinoma of thyroid cases

had association with Hashimoto's thyroiditis [20]. Similar findings were observed by Resende D Paiva C et al., [21].

The present study proved an association between Hashimoto's thyroiditis and papillary carcinoma. Patients who had papillary carcinoma of thyroid were more likely to have Hashimoto's thyroiditis. Konturek A et al., and Larson SD et al., also found a similar association [6,22]. The first study that established an association between Hashimoto's thyroiditis and papillary carcinoma of thyroid dates back to 1955 [23]. On the contrary, Matesa-Anic D et al., and Mazokopakis EE et al., did not observe any significant association between Hashimoto's thyroiditis and papillary carcinoma of thyroid [8,12]. The possible explanation of contradiction can be coincidence or selection bias.

The strength of the study was that data was extracted from the clinical case records of the patients from a single Institution and on final histopathological reports done by pathologists, thereby reducing the observer bias.

Limitation(s)

Being a retrospective record-based study, the availability and content of the medical records was a concern, due to which lymph node metastasis and genetic parameters could not be studied. Prospective studies are needed to strengthen the findings of the present study and also to understand the pathophysiologic mechanism of Hashimoto's thyroiditis transforming into thyroid carcinomas.

CONCLUSION(S)

In the present study, benign thyroid disease followed by papillary carcinoma of thyroid was the most common indications for thyroidectomy. Sex of the patient was found to be associated with Hashimoto's thyroiditis. The findings revealed that the patients who had papillary carcinoma of thyroid were more likely to have Hashimoto's thyroiditis in comparison to the patients without papillary carcinoma of thyroid.

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