

## Original Research Article

# Hashimoto's thyroiditis-a tertiary level hospital based study

Ganesh Manikantan, Meer M. Chisthi\*

Department of General Surgery, Government Medical College, Calicut, Kerala, India

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**\*Correspondence:**

Dr. Meer M. Chisthi,

E-mail: [meerchisthi@gmail.com](mailto:meerchisthi@gmail.com)

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### ABSTRACT

**Background:** Hashimoto's disease is a chronic, autoimmune form of thyroiditis and is one of the most common causes for hypothyroidism. Many studies have found an association between Hashimoto's thyroiditis and various other thyroid pathologies, including cancers. The objectives of the study were to look for any association between Hashimoto's thyroiditis and other forms of thyroid diseases and to analyse the pattern of patients treated with Hashimoto's thyroiditis.

**Methods:** This was a retrospective study conducted at a tertiary care centre from December 2008 to January 2014. Patients with Hashimoto's thyroiditis confirmed by histology were selected as the cases. Their clinical and biochemical data and post-operative histopathological reports were collected and analysed.

**Results:** 300 patients who underwent thyroidectomy were found to have a diagnosis of Hashimoto's thyroiditis. 97.33% of the patients were females. Maximum patients belonged to the 31-40 age group. Of the 300 patients, 61.67% had other associated pathologies. The maximum association was with colloid goiters, followed by adenomas and malignancies. Among the malignancies, 80.65% were papillary cancers while the rest were follicular cancers. There were no cases of other malignancies associated with Hashimoto's thyroiditis.

**Conclusions:** Hashimoto's thyroiditis is fairly common in the studied population, mostly among females. It is associated with other thyroid pathologies including differentiated cancers. Lymphoma is not found to be associated with Hashimoto's disease in our population. Hashimoto's thyroiditis thus forms a major share of goiters leading to thyroidectomy in Indian population. However, the decision to operate should be primarily governed by the associated cytology.

**Keywords:** Hashimoto's disease, Papillary thyroid cancer, Thyroiditis, Thyroidectomy, Thyroxine

### INTRODUCTION

It was in 1912 that Dr. Hakaru Hashimoto described "lymphomatous changes of the thyroid." Since then, chronic autoimmune thyroiditis has been linked to his name and is commonly referred to as Hashimoto's thyroiditis.<sup>1</sup> Hashimoto's thyroiditis is a chronic, organ-specific autoimmune disease, affecting more than 10% of females and 2% of males. It is one of the most common causes of primary hypothyroidism during the adolescent period, via autoimmune thyroid tissue destruction. The pathogenesis of Hashimoto's disease involves a somewhat complex interaction between predisposing

genetic and environmental factors even though the pattern of inheritance is non-Mendelian.<sup>2</sup> Circulating antibodies directed against thyroid peroxidase (TPO-Ab) are found in abundance in Hashimoto's thyroiditis. Studies have reported that the thyroid cell damage and death, in patients with Hashimoto's thyroiditis is due to anti-TPO antibodies as well as Th1 cytokines.<sup>3,4</sup> As per some authors, Hashimoto's thyroiditis and Graves' disease are different expressions of a basically similar autoimmune process, and the clinical behaviour reflects the spectrum of the immune response in any particular patient.<sup>2</sup> During this response, various responses including cytotoxic auto-antibodies, stimulatory auto-

antibodies, blocking auto-antibodies, or cell-mediated auto-immunity may be observed. Persons with classic Hashimoto's thyroiditis are found to have serum antibodies reacting with thyroglobulin as well as thyroid peroxidase.

Hashimoto's thyroiditis is an autoimmune inflammatory disease characterized by widespread lymphocyte infiltration, fibrosis, and later parenchymal atrophy.<sup>5</sup> The diagnosis is almost certain when antibodies to thyroid peroxidase enzyme and thyroglobulin are present in the circulation in a patient with hypothyroidism but the presence of diffuse lymphocytic infiltrates, lymphoid follicles with reactive germinal centers, parenchymal atrophy, and fibrosis on histology clinch diagnosis of Hashimoto's in truest sense.<sup>6</sup> On a high-resolution ultrasonography, this entity is commonly seen as diffusely enlarged, heterogeneous, and hyper-vascular thyroid gland with micronodules, echogenic septations, and reduced echogenicity.<sup>7,8</sup>

Therapeutic strategies in Hashimoto's thyroiditis include levothyroxine alone or in combination with selenium.<sup>9,10</sup> Mariotti et al studied a group of hypothyroid as well as euthyroid patients with Hashimoto's and detected a significant decrease in TPO-Ab after 1-1 1/2 years of levothyroxine therapy in most patients.<sup>11</sup>

This is in accordance with observations of Schumm-Draeger et al who also found a significant reduction in TPO-Ab in euthyroid patients with Hashimoto's thyroiditis treated with levothyroxine.<sup>12</sup> Some studies have also addressed the decrease in TPO-Ab under additional selenium therapy in addition to levothyroxine.<sup>13,14</sup> Gartner et al demonstrated that, in his group of patients with Hashimoto's who were treated with 200 mg of sodium selenite per day, a significant decrease of TPO-Ab to 63.6% of the initial levels occurred within 3 months of treatment.<sup>10</sup>

A better understanding of the histological pattern of patients with Hashimoto's thyroiditis will definitely add to the existing knowledge on this common pathology. With this background, we studied the clinical and histological profile of patients who had a pathological diagnosis of Hashimoto's thyroiditis after thyroidectomy. The primary objective of the study was to look for any association between Hashimoto's thyroiditis and other forms of thyroid diseases among patients who underwent thyroidectomy at our institution over the 5-year study period. The secondary objective was to analyse the histological as well as clinical pattern of these patients.

## METHODS

This study was designed as a hospital based retrospective cohort study. The study setting was the General Surgery wards of Government Medical College Trivandrum. This is one of the biggest medical colleges in the public sector in the state of Kerala. Our institution is attended by a

large number of patients from the southern districts of both Kerala and Tamil Nadu states. The study period was for 5 years, from December 2008 to January 2014. The study subjects included all patients who underwent elective thyroidectomy at our institution during the study period of 5 years and were subsequently detected to have Hashimoto's disease by pathological analysis.

Inclusion criteria consisted of all patients aged between 12 to 80 years who underwent thyroidectomy for any indication and were diagnosed with Hashimoto's thyroiditis. Consecutive sampling method was employed. All consecutive patients who fulfilled the eligibility criteria were enrolled into the study. Institutional Research Committee clearance was obtained and approval from the Human Ethics Committee of the institution was obtained before starting the study.

From the Medical Records library of our institution, information was collected about patients who underwent thyroidectomy for all indications and were detected to have Hashimoto's disease. The case-sheets of all these patients were collected and relevant information recorded from them. Clinical presentation, investigation results, pathological diagnosis and the treatment modalities were analyzed. The variables recorded included demographic details, anthropometric data and details of symptoms and signs. Intra-operative findings as well as postoperative details regarding the histopathological examination were also recorded into the proforma.

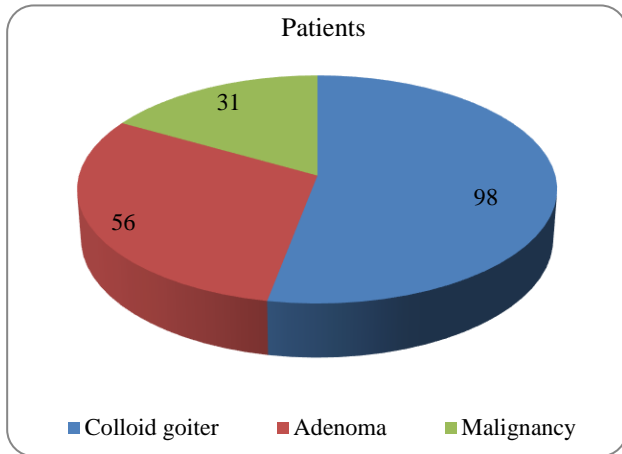
All collected data were entered a structured proforma. For statistical analysis, 'Epi Info' by the CDC (Centers for Disease Control and prevention) was the software used. Quantitative data is described as means plus standard deviation and categorical data is listed as percentages. If and where relevant, the level of statistical significance was set at any p value less than 0.05.

## RESULTS

The study was conducted on patients who underwent thyroidectomy over a 5-year period and were diagnosed to have Hashimoto's disease. The study was aimed at finding the various histopathological patterns seen in Hashimoto's thyroiditis and the various associations with other pathologies. At the end of the study, 300 patients who underwent thyroidectomy were studied. Among the 300 patients, except for 8 males, all others were females (97.33%). The effective male: female ratio was calculated to be 1:36.6. Maximum patients were seen to fall in the 31-40 age group.

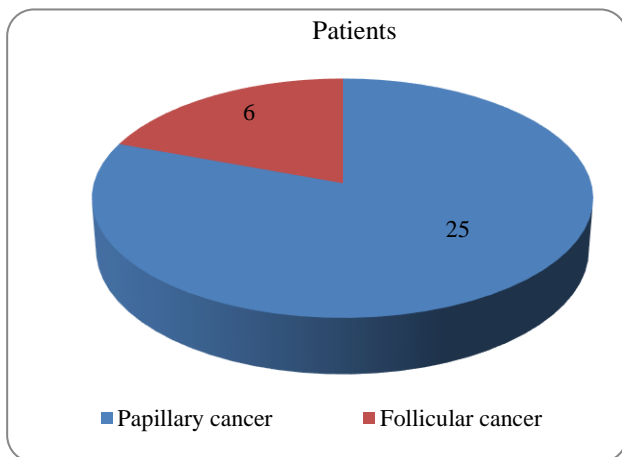
There was no definite association with any form of altered hormonal status as the patients were seen to have all forms of thyroid status including hypothyroid and euthyroid and corrected hyperthyroid states. Also, it was found that Fine Needle Aspiration Cytology (FNAC) could detect Hashimoto's thyroiditis preoperatively in as high as 70% of the cases.

Of the 300, 185 patients (61.67%) had Hashimoto's thyroiditis associated with other pathologies (Figure 1).



**Figure 1: Distribution of other pathologies associated with Hashimoto's thyroiditis.**

Among these 185 patients, the maximum cases (98) had associated colloid goiters (32.67%) while 56 (18.67%) had associated adenomas and 31 had malignancies (10.33%). Among the 31 patients with malignancies, 25 (80.65%) patients had associated papillary thyroid cancer while the remaining 6 (19.35%) had follicular type of thyroid cancer (Figure 2). Among those with associated malignancies, papillary cancer was seen mostly in patients belonging to the 31-40 years age group whereas follicular cancer was seen maximum in patients from the 51-60 years age group. There were no cases of other malignancies like medullary, anaplastic or lymphoma which were found to be associated with Hashimoto's thyroiditis.



**Figure 2: Distribution of malignancies associated with Hashimoto's thyroiditis**

## DISCUSSION

This retrospective study looked at the association of Hashimoto's thyroiditis with other thyroid pathologies as

assessed following thyroidectomy. As per our study, thyroiditis mostly affects females which is quite evident from the very high female to male ratio seen in goiter patients from India, especially in South India. Regarding the associated pathologies, colloid goiter was the commonest association which is explained by the fact that colloid goiters form the commonest indication for thyroidectomy in our country. Among the malignancies, papillary and follicular were the only thyroid cancers found to be associated with Hashimoto's disease.

The relationship between Hashimoto's and papillary carcinoma was first proposed by Dailey et al in their 1955 report.<sup>15</sup> Since that report, the association between these two diseases has remained controversial, with some studies reporting up to 38% concurrence rate.<sup>16,17</sup> Singh et al and Loh et al reported that papillary cancer patients with Hashimoto's were two or three years younger than those without. Repplinger et al reported that females with Hashimoto's were 30% more likely to have coexisting papillary cancer compared with other females.<sup>18-20</sup> However, some authors have refuted this claim. Crile found only one case of papillary cancer in a population based follow up study of 200 patients with Hashimoto's.<sup>21</sup> The revised American Thyroid Association (ATA) guidelines for thyroid nodules also has reported that the rate of malignancy in nodules among thyroid glands involved with Hashimoto's is possibly higher.<sup>22</sup>

A number of proposed mechanisms in the literature explain the relationship between Hashimoto's thyroiditis and papillary carcinoma. In 1972, McConahey proposed that chronic stimulation of the thyroid by the elevated TSH levels may initiate or promote the growth of thyroid neoplasm.<sup>23</sup> Wirtschafter et al identified expression of the RET/PTC1 and RET/PTC3 oncogenes in patients with Hashimoto's.<sup>24</sup> Recently, Larson et al reported increased PI3K/AKT expression in both Hashimoto's and well-differentiated thyroid cancers, suggesting a possible mechanism for carcinogenesis.<sup>25</sup> Currently another hypothesis considered for pathogenesis of papillary cancer in Hashimoto's thyroiditis is solid cell nest (SCN), which measure 0.1 mm or less in diameter and consist of polygonal to ovoid cells with elongated nuclei, finely granular chromatin, and may show nuclear grooves.<sup>26</sup> SCN may be misinterpreted as papillary thyroid microcarcinoma, squamous metaplasia of follicular thyroid cells, primary or metastatic squamous cell carcinoma, thyroglossal cyst, C-cell hyperplasia, and medullary microcarcinoma. The distinction between these lesions and SCN can sometimes be made based on the hematoxylin and eosin (H and E) appearance, but often needs immunohistochemistry for confirmation. Histologically, Hashimoto's disease concurrent with papillary cancer appears more hypoechoic, with well-defined margins as well as lobulations.

Recent literature suggests a protective effect of Hashimoto's in patients with papillary cancer. In a large

retrospective study, Kashima et al reported a 0.7% cancer specific mortality and a 95% relapse-free 10-year survival rate in patients with chronic thyroiditis compared to a 5% mortality and 85% relapse-free 10-year survival rate in those without.<sup>27</sup> Loh et al and Singh et al also identified a positive correlation between patients with Hashimoto's and papillary cancer and disease-free survival and overall survival.<sup>18,19</sup> Recently, Kim et al assessed the clinical impact of coexisting chronic lymphocytic thyroiditis with thyroid cancer and found that it was associated with smaller tumour size at presentation and also a reduced risk of recurrence.<sup>28</sup>

Mechanisms for a better prognosis in patients with papillary cancer with Hashimoto's thyroiditis have been hypothesized in different ways. Giodarno et al reported that follicular cells in Hashimoto's express both Fas and Fas ligands that probably activate the Fas-mediated apoptotic pathway and cause destruction of the thyroid tissues.<sup>29</sup> As papillary cancer cells originating from the follicular cells would express thyroid specific antigens, auto-antibodies from coexisting Hashimoto's might destroy the tumour cells in much the same way as normal cells.<sup>30</sup>

Additionally, the infiltrated lymphocytes in patients with Hashimoto's are likely to be cytotoxic T cells secreting interleukin-1 that inhibit thyroid cancer cell growth.<sup>31</sup> Kim et al reported a significantly lower prevalence of BRAF V600E mutation in patients with Hashimoto's thyroiditis and papillary cancer, explaining the better prognosis.<sup>32</sup> Patients with papillary carcinoma and coexisting Hashimoto's thyroiditis have lower stage disease at the time of their surgery, possibly because the cancer gets picked up earlier as majority of these patients may be under follow up for hypothyroidism.<sup>33</sup>

As per established literature, the malignancy which is strongly associated with Hashimoto's disease is lymphoma. Holm et al showed that Hashimoto's has increased association only with lymphoma and that in patients with Hashimoto's, the risk of primary thyroid lymphoma is supposedly increased by a factor of 67.<sup>16</sup> Nonetheless, some authors say that primary thyroid lymphoma is only a rare complication of Hashimoto's disease. Several investigators have reported an association between Hashimoto's disease and medullary cancer of thyroid, most of which are case reports.<sup>34,35</sup> Segal et al surprisingly reported seven cases of Hashimoto's thyroiditis associated with 4 different types of thyroid carcinoma: of these, 3 of the cases were follicular carcinoma, two were mixed papillary and follicular carcinoma, one was anaplastic cancer, and one was medullary.<sup>36</sup>

Total thyroidectomy with an optional lymph node dissection is the treatment of choice for Hashimoto's thyroiditis when it coexists with papillary thyroid carcinoma.<sup>37,38</sup> The presence of Hashimoto's disease does not alter the management and extent of surgery in

papillary cancer and the treatment is no different when matched for stage and type.<sup>39</sup> Interestingly, it is worthwhile to mention that the ultimate tool to correct thyroid hormone deficiency in a patient with Hashimoto's disease, who does not have a functional thyroid gland, could be thyroid transplantation.<sup>40</sup> Although no longer just a far-fetched dream, it does still remain an idea with a futuristic approach.

Our study does have a few limitations. The primary issue is that the retrospective study design limits the possibilities for statistical analysis. Also, a better design for checking associations would have been case-control with inclusion of matched controls. Nevertheless, we were able to elucidate enough information from our data, especially in view of the rather high sample size in the study.

## CONCLUSION

To conclude, Hashimoto's thyroiditis is fairly common in our setting. It is found predominantly in females from the young to middle age groups. This disease is found commonly in association with other pathologies including colloid goiters and cancers. As opposed to other populations, Hashimoto's disease is found to be associated with mostly papillary cancer and follicular cancer less commonly in our patients. As a corollary, as is evident from the literature, the decision to operate should be based on the presence of co-existing cytological conditions or pressure effects and not primarily on the diagnosis of Hashimoto's thyroiditis.

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