ORIGINAL ARTICLE

FREQUENCY OF HASHIMOTO THYROIDITIS IN PAPILLARY THYROID CANCER PATIENTS AND ITS IMPACT ON THEIR OUTCOME

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Background: Hashimoto thyroiditis (HT) is an autoimmune disorder of thyroid gland and is the most common cause of hypothyroidism. Its association with thyroid lymphoma is well established but with papillary thyroid cancer (PTC), the studies have shown inconsistent results. **Methods:** It is a retrospective review of papillary thyroid cancer patients and 213 participants were included for final analysis. They were divided in two groups, based on presence or absence of Hashimoto thyroiditis. We noted their demographic details, histopathological diagnosis, presence of thyroid autoantibodies, TNM staging, outcome and duration of follow up. **Results:** The frequency of Hashimoto thyroiditis in papillary thyroid cancer patients was found to be 34.27% (73). In Hashimoto thyroiditis and PTC patients, more patients were in T1 and T2 stage, i.e., 27.4% and 38.4% as compared to PTC alone group, who had more patients with T3 and T4 disease 44.3% and 5% respectively. Although lymph node metastasis was more common in PTC with Hashimoto thyroiditis 56.2%, but distant metastasis was observed more in isolated PTC group 14.3%. Cure was observed in 75.3% and 47.1% in PTC patients with and without Hashimoto thyroiditis respectively. While 22.9% patients having isolated PTC had persistent disease as compared to 6.8% when PTC was accompanied with Hashimoto thyroiditis. **Conclusion:** The papillary thyroid cancer patient who had concomitant Hashimoto thyroiditis, had a less aggressive disease in terms of T stage and distant metastasis and they had a better outcome in terms of higher cure rate and less persistent disease as compared to the papillary thyroid cancer without Hashimoto thyroiditis.

Keywords: Hashimoto thyroiditis (HT); Papillary thyroid cancer (PTC); TNM staging

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INTRODUCTION

Hashimoto thyroiditis (HT), an autoimmune disorder, is a common cause of hypothyroidism. Its incidence is reported to be 0.3–1.5 cases per 1000 persons and it commonly affects females. However, the incidence is variable across the world depending upon the geographical distribution, environmental factors and iodine deficiency.[1,2] Its pathogenesis is characterized by the presence of autoantibodies and abnormal cellular response directed against the thyroid autoantigen. This led to chronic inflammation and destruction of thyroid gland.[2] The autoantibodies involved are anti-thyroid peroxidase antibodies (anti-TPO) and anti- thyroglobulin antibodies (anti-TG). These are also used for diagnosis of Hashimoto thyroiditis.[3]

An initial concept of chronic inflammation leading to neoplasia was proposed by Virchow in 1863. Since then, this relationship is well established in various cancers like inflammatory bowel disease and colon cancer.[2] Similarly, Hashimoto thyroiditis has also been extensively investigated to be a cause of differentiated thyroid cancers, mainly papillary thyroid cancer (PTC). Its association with the thyroid lymphoma is well established. The risk of thyroid lymphoma rises to as high as 80 folds in the presence of Hashimoto thyroiditis.[2] Hashimoto thyroiditis as a risk factor for papillary thyroid cancer was first suggested by Daily *et al* in 1955.[1] Till now the results of studies done to prove this association are inconsistent.

Thyroid cancer is the most common endocrine malignancy, and its incidence is on the rising trend. Around 34000 patients are diagnosed with thyroid cancer in USA each year.[4] Just like Hashimoto thyroiditis, thyroid cancer affects more females than males. It is divided into differentiated thyroid cancer (DTC) which is most common, followed by medullary (5–8%) and anaplastic thyroid cancer (<5%).[1] Differentiated thyroid cancer is further subdivided into papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC). Hashimoto thyroiditis is linked with the increased risk of differentiated thyroid cancers mainly papillary carcinoma.[5]

In this study we aimed to determine the frequency of Hashimoto thyroiditis in patients

diagnosed as papillary thyroid cancers. Moreover, the patients who have both the conditions together will then be compared to the those who have isolated PTC, in terms of tumour stage, tumour size, lymph node involvement, distant metastasis and outcomes. This would help us understand whether Hashimoto thyroiditis is associated with the higher stage of disease or more aggressive tumour with metastasis.

MATERIAL AND METHODS

It is a retrospective review of patients who got admitted with the diagnosis of papillary thyroid cancer from 1st Jan 2009 to 31st December 2018 at Aga Khan University Hospital. This Hospital is a tertiary care unit located in Karachi, Pakistan**.** After getting approval from the Ethical review board (ERC number: 2019-0950-2427)**,** we analyzed the data of 213 patients. We noted their demographic details, reviewed the diagnosis, and confirmed the presences of Hashimoto thyroiditis either by histopathology or presence of autoantibodies. These antibodies included anti-thyroid peroxidase (Anti-TPO) antibodies or anti-thyroglobulin (Anti-TG) antibodies. We also noted the stage of tumour, involvement of lymph nodes and presence of any distant metastasis. For these parameters, in addition to histopathology review, we checked if any ultrasound neck, CT scan or diagnostic or post therapeutic I^{131} scan was done.

The outcome was classified as either cured or persistent disease. Cured was defined as absence of any evidence of local or distant metastatic disease on imaging, i.e., ultrasound neck, I^{131} scan or CT scan. Another criterion for cure was unstimulated thyroglobulin (TG) levels less than 1ng/ml or stimulated thyroglobulin levels less than 0.2 ng/ml, in the absence of interfering anti-thyroglobulin antibodies, after initial curative surgery and radioactive iodine (RAI) treatment.[6] Persistence was labelled in cases who never got cured after potentially curative surgery and radioactive iodine therapy. They either had structural residual disease or have persistently elevated thyroglobulin level in the absence of interference by anti-thyroglobulin antibodies with or without radiological evidence of the disease. Follow up duration was also noted in months and all the included patients were above age 18 years.

First the frequency of Hashimoto thyroiditis was noted. Secondly, we noted tumour size, stage, local and distant metastasis, and outcome of the tumour. Then, a comparison was done between patients of papillary thyroid cancer who had concomitant Hashimoto thyroiditis and those who did not have Hashimoto thyroiditis.

For independent categorical variables including gender, presence of Hashimoto thyroiditis, stage of tumour, presence of metastasis and outcome, frequency with percentage was reported. For continuous variables like age and follow up duration, either mean with standard deviation (SD) (if the normality assumption was met) or median with interquartile range (IQ) was reported. For comparison between the variables, multiple logistic regression was used, and Backward-Wald method was applied. *p*-value of <0.05 was considered statistically significant.

RESULTS

Hashimoto thyroiditis (HT) was identified in 73 (34.27%) of patients. Mean age was comparable in PTC patients with or without hashimoto thyroiditis i.e., 40.88±15.58 and 41.44±15 years and in both cases, and majority were female 58 (79.5%) and 84 (60%) respectively. The size of tumour was 3.67±2.87 cm in patients who had PTC while it was 3.05±1.81 cm in patients who had both PTC and Hashimoto thyroiditis.

In patients of PTC who had concomitant HT, staging of disease showed 20 (27.4%) were at stage T1, 28 (38.4%) at T2, 22 (30.1%) at T3 and 3 (4.1%) were at T4 stage. On the other hand, the patients who did not have co-existing HT, 43 (30.7%) had T1 disease while 28 (20%), 62 (44.3%) and 7 (5%) had stage T2, T3 and T4 respectively.

The lymph nodes metastasis was observed in 61 (43.6%) of isolated PTC while it was found in 41 (56.2%) in the presence of HT. A total of 21 patients had distant metastasis. Out of which, only 1 (1.4%) patient had HT along with PTC.

In terms of outcome, 66 (47.1%) of isolated PTC were cured while 32 (22.9%) had persistent disease. In the presence of HT with PTC, 55 (75.3%) and 5 (6.8%) were cured and had persistent disease respectively. There were 42 (30%) patients who had followed up record of less than six months among isolated PTC patients while 13 (17.8%) of PTC and HT patients were lost to follow up. Mean duration of follow up was 17 (3–41) months.

When the PTC patients who had co-existing HT were compared with Isolated PTC, it was found that they had less aggressive disease in terms of T staging. Although lymph nodes metastasis was observed more commonly in HT group, (56.2% vs 43.6%) (*p*-value 0.005), distant metastasis was observed only in 1 patient who had HT with PTC, while it was found in 20 patients who had isolated PTC. In terms of outcome, more patients were cured if they had HT co-existing with PTC (*p*-value 0.01).

Variables entered in the model: age, gender, size of tumour, focality, T stage, lymph nodes, distant metastasis, outcome, follow-up length Backward-Wald method was applied, *p*-value<0.05 considered to be statistically significant.

Table-1: Demographic details

Parameters	Total no. of patients (n = 213)	Papillary thyroid cancer patients without Hashimoto thyroiditis (n = 140)	Papillary thyroid cancer patients with hashimoto thyroiditis (n = 73)
Age (years) mean ± SD	41.24 ±15.17	41.44 ± 15	40.88 ± 15.58
Gender			
Male	71(33.3%)	56(40%)	15(20.5%)
Female	142(66.7%)	84(60%)	58(79.5%)
T stage			
T1	63(29.6%)	43(30.7%)	20(27.4%)
T2	56(26.3%)	28(20%)	28(38.4%)
T3	84(39.4%)	62(44.3%)	22(30.1%)
T4	10(4.7%)	7(5%)	3(4.1%)
Lymph nodes metastasis			
No	111(52.1%)	79(56.4%)	32(43.8%)
Yes	102(47.9%)	61(43.6%)	41(56.2%)
Distant metastasis			
No	192(90.1%)	120(85.7%)	72(98.6%)
Yes	21(9.9%)	20(14.3%)	1(1.4%)
Outcome			
Cured	121(56.8%)	66(47.1%)	55(75.3%)
Persistent	37(17.4%)	32(22.9%)	5(6.8%)
No f/u	55(25.8%)	42(30%)	13(17.8%)
Size of tumor (cm) mean ± SD	3.46 ± 2.57	3.67 ± 2.87	3.05 ± 1.81
Follow up duration (months)	17(3–41)	15(0–39.75)	24(11–53)

Table-2: Multiple logistic regression

Variable	OR (95% CI)	*p*-value
Gender		
Male	1	
Female	3.084 (1.492–6.376)	0.002
Lymph node metastasis		
No	1	
Yes	2.545 (1.321–4.904)	0.005
Outcomes		
No f/u	1	
Cured	2.696 (1.270–5.723)	0.010
Persistent	0.417 (0.124–1.396)	0.156

DISCUSSION

Hashimoto thyroiditis being an autoimmune disease, is 20 times more common in females and similarly PTC also affects females 2.9 times more than the males. Same was observed in our study where majority of patients were female. However, the proportion of female population was significantly higher in PTC with HT (79.5%) as compared to PTC alone (60%) (*p*-value 0.002). This female predominance has been consistently observed in different areas and ethnicity. Although very few studies have actually looked into the cause of this gender disparity, these were unable to describe any genetic or environmental factors responsible.[7]

Mean age of patients with isolated PTC and those having both PTC and HT, was comparable as 41.44±15 and 40.88±15.58 years respectively. This is different from other reported data where patients with PTC and HT were younger at the time of presentation.[8] Although, in another study when age group <45 years and >45 years were compared for the frequency of PTC co-existing with HT, there was no significant difference.[9]

HT co-existing with PTC was observed in 73 (34.27%) of participants. In different studies, the presence of HT with PTC patients is variable, ranging from 0.5–38%.[10] HT is found to be 2.4 times more common in PTC than other thyroid cancers.[11] In one study HT was present in 28.6% of patients who underwent surgery for PTC, while it was observed in only 7.7% of those who had thyroidectomy for other reasons**.** Similarly, 31.3% of patients who had HT, were diagnosed with PTC.[12] Anti-thyroid antibodies (anti-TPO and anti-TG antibodies) are also associated with increased risk of malignant transformation in thyroid nodules and as a specific risk factor for PTC.[2] In patients who had fine needle aspiration cytology (FNAC) for thyroid nodule, the prevalence of thyroid malignancy was 13.7% in anti-thyroid antibodies positive patients as compared to 8.4% in anti-thyroid antibodies negative ones. In anti-thyroid antibodies positive patients, the type of thyroid tumour was PTC in 96.3% of cases.[13] The existence of both entities, i.e., HT and PTC together points towards a possible association between the two and HT has been hypothesized as a risk factor for PTC. However, multiple other studies have shown different results. A metanalysis of population based FNAC studies has shown no significant association between the two.[14]

The exact pathophysiology explaining this relationship is still unclear. Chronic inflammation leading to neoplastic transformation has been recognized in other cancers like gastric, colorectal, and head and neck cancers. Similarly, in HT chronic

active inflammation characterized by lymphocytic infiltration, generates oxygen free radicals which can trigger mutations and tumorigenesis.[15] HT has been even described as pre-cancerous condition by some authors and is considered as a risk factors for other malignancies as well, like colorectal cancer especially in Asian population.[16] A study has shown increased expression of cyslooxygenase-2 (COX-2) in HT cases and this increased COX-2 has also been observed in thyroid cancer cells. This enzyme is thought to be involved in early steps of malignant transformation in thyroid follicles.[16] The BRAF mutation and RET/PTC alterations found in PTC are also seen in HT, conferring to some common pathology at molecular level.[3] Hypothyroidism and elevated TSH levels caused by HT has also been linked with proliferation of thyroid follicular cells and development of PTC. This was supported by Fiore *et al*, who showed high TSH levels caused PTC in nodular variant of HT. But later studies have not found such association.[17] So, the results of different studies are variable and the main drawback of many studies including ours, is retrospective nature of data where known patients of PTC or those who underwent thyroidectomy were included, causing a selection bias. Mostly the studies based of thyroidectomy data show a positive correlation between PTC and HT while those based on FNAC data suggest no such relationship.[10]

In terms of TNM staging, more patients of PTC with HT were found in stage T1 and T2 (27.4% and 38.4%) as compared to isolated PTC (30.7% and 20%). Similarly, in T3 and T4, the number of patients was higher who had isolated PTC than PTC co-existing with HT, i.e., 44.3% and 5% vs 30.1% and 4.1%. This observation is interesting as HT is being investigated to be a cause of PTC, but at the same time patients with HT and PTC were found to have less aggressive disease. This finding was also observed in some other studies as well where PTC and HT was found to have lower stage of tumour and good outcome overall.[12] This can be explained by the fact that HT patients are usually under follow up for hypothyroidism and malignancy can be picked up at an early stage.

There size of tumour was not very conspicuous between the two group of patients. It has been reported previously that presence of HT with PTC does not affect the primary tumour foci, despite associated with less extrathyroidal extension, lymph node or distant metastasis and favourable outcomes.[9]

In terms of local metastasis, PTC with HT was associated with slightly higher number of lymph node involvement. Isolated PTC metastasized to lymph nodes in 61 (43.6%) patients, while it was observed in 41 (56.2%) of PTC and HT. This difference is statistically significant (*p*-value 0.005). The co-existence of HT and PTC has been associated with limited or even absent lymph node involvement.[11] But this has not been observed in our study.

On the other hand, distant metastasis was observed in 20 (14.3%) of isolated PTC patients and only 1 (1.4%) of PTC with HT. This finding was further supported by the fact that majority of patients with PTC and HT were cured 55 (75.3%) and it was statistically significant (*p*-value 0.01). In comparison, cure was observed only in 66 (47.1%) of patients having PTC alone. Similarly, persistent disease was found in only 5 (6.8%) patients having both PTC and HT while it was present in 32 (22.9%) of patients who had PTC only. Low grade tumour with less distant metastasis complies with the higher cure rate and good prognosis. There is heterogeneity of data for outcomes of PTC with HT. Multiple studies have shown the same results as ours, that PTC with co-existing HT was associated with small tumour, minimal or no extra thyroid extension and better disease-free survival.[11,14] However, few investigators have also documented that presence of HT does not affect the prognosis of PTC.[8,9]

Mean duration of follow up in our patients was 17 (3–41) months. The patients who had less than six months follow up record were 42 (30%) and 13 (17.8%) in isolated PTC and PTC with HT group respectively.

The variation in results could be because of different criteria used for diagnosis of HT, variable impact of HT on different populations and different age groups.[8] Moreover, due to retrospective nature of data, possibility of missed reporting of HT in the presence of PTC cannot be excluded. Although the exact pathophysiology involved in good outcomes of PTC in the presence of HT, is still unclear. It has been postulated that inflammation caused by HT and autoantibodies have antitumor effects. They prevent the growth and dissemination of neoplastic cells in the thyroid.[15] There is another theory that suggests that lymphocyte infiltration used for the histopathological diagnosis of HT, is in fact caused by tumour itself.[9] It represents an immune response and helps to control proliferation of neoplastic cells.

CONCLUSION

In conclusion, in our study, HT was found in significant number of papillary thyroid cancer patients. However, it is difficult to say that HT is a causative factor for PTC. As both PTC and HT are common in female, their incidental co-existence cannot be ruled out. We need further prospective studies to establish this association. However, we did

find that the presence of HT is associated with less distant metastasis and higher cure rate of PTC.

Our study has limitations as it is a retrospective study in a single centre and known patients of PTC were included. Moreover, our institution mainly serves the urban population. So due to the selection bias, the results may not be generalizable to whole Pakistani population. There were many patients for whom the follow up record was not available. This represents a lack of awareness and financial constraints, because of which thyroid cancer patients could not maintain follow up in clinics. Moreover, clinicians need to educate patients regarding the good prognosis of PTC especially if it co-exists with HT, provided early treatment and regular follow up is done.

AUTHORS' CONTRIBUTION

SB: had the concept of study and conceptualize the study design, she was involved in data analysis, did the literature search and write-up. BD: Helped in data collection and manuscript writing especially introduction and discussion. MHA: Did the data collection, data analysis and literature rev review. NJ: was involved in manuscript writing and proof reading.

REFERENCES

1. Resende de Paiva C, Grønhøj C, Feldt-Rasmussen U, von Buchwald C. Association between Hashimoto's Thyroiditis and Thyroid Cancer in 64,628 Patients. Front Oncol 2017;7:53.
2. Azizi G, Keller JM, Lewis M, Piper K, Puett D, Rivenbark KM, *et al*. Association of Hashimoto's thyroiditis with thyroid cancer. Endocr Relat Cancer 2014;21(6):845–52.
3. Anand A, Singh KR, Kushwaha JK, Hussain N, Sonkar AA. Papillary Thyroid Cancer and Hashimoto's Thyroiditis: An Association Less Understood. Indian J Surg Oncol 2014;5(3):199–204.
4. Thyroid Carcinoma [Internet]. [cited 2019 Jan 8]. Available from: http://jpma.org.pk/full_article_text.php?article_id=3007
5. Boi F, Pani F, Mariotti S. Thyroid Autoimmunity and Thyroid Cancer: Review Focused on Cytological Studies. Eur Thyroid J 2017;6(4):178–86.
6. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al*. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26(1):1–133.
7. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncol 2010;6(11):1771–9.
8. Babli S, Payne RJ, Mitmaker E, Rivera J. Effects of Chronic Lymphocytic Thyroiditis on the Clinicopathological Features of Papillary Thyroid Cancer. Eur Thyroid J 2018;7(2):95–101.
9. Dobrinja C, Makovac P, Pastoricchio M, Cipolat Mis T, Bernardi S, Fabris B, *et al*. Coexistence of chronic lymphocytic thyroiditis and papillary thyroid carcinoma. Impact on presentation, management, and outcome. Int J Surg 2016;28(Suppl 1):S70–4.
10. Deligiorgi MV, Trafalis DT. Papillary Thyroid Carcinoma Intertwined with Hashimoto's Thyroiditis: An Intriguing Correlation. Knowledges on Thyroid Cancer [Internet]. 2019 Apr 10 [cited 2020 Aug 12]; Available from: https://www.intechopen.com/books/knowledges-on-thyroid-cancer/papillary-thyroid-carcinoma-intertwined-with-hashimoto-s-thyroiditis-an-intriguing-correlation
11. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol 2013;168(3):343–9.
12. Graceffa G, Patrone R, Vieni S, Campanella S, Calamia S, Laise I, *et al*. Association between Hashimoto's thyroiditis and papillary thyroid carcinoma: a retrospective analysis of 305 patients. BMC Endocr Disord 2019;19(1):26.
13. Boi F, Lai ML, Marziani B, Minerba L, Faa G, Mariotti S. High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies. Eur J Endocrinol 2005;153(5):637–42.
14. Jankovic B, Le KT, Hershman JM. Clinical Review: Hashimoto's thyroiditis and papillary thyroid carcinoma: is there a correlation? J Clin Endocrinol Metab 2013;98(2):474–82.
15. Lai X, Xia Y, Zhang B, Li J, Jiang Y. A meta-analysis of Hashimoto's thyroiditis and papillary thyroid carcinoma risk. Oncotarget 2017;8(37):62414–24.
16. Chen YK, Lin CL, Cheng FTF, Sung FC, Kao CH. Cancer risk in patients with Hashimoto's thyroiditis: a nationwide cohort study. Br J Cancer 2013;109(9):2496–501.

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