

THYROID

Hashimoto's thyroiditis in papillary thyroid carcinoma: a 22-year study

Tiroidite di Hashimoto nel carcinoma papillare della tiroide: studio di 22 anni

Fatih Mehmet Hanege¹, Ozan Tuysuz¹, Serdal Celik¹, Oner Sakalliglu², Ozgen Arslan Solmaz³

¹ Istanbul Medeniyet University, School of Medicine, Department of Otorhinolaryngology and Head & Neck Surgery, Goztepe Training and Research Hospital, Istanbul, Turkey; ² Elazig Health Practices and Research Center, Department of Otorhinolaryngology and Head & Neck Surgery, Elazig, Turkey; ³ Elazig Fethi Sekin City Hospital, Department of Pathology, Elazig, Turkey

SUMMARY

Objective. We retrospectively investigated whether there is a relationship between Hashimoto's thyroiditis (HT) and papillary thyroid carcinoma and studied the effect of HT on prognostic factors.

Methods. 1080 patients, who underwent thyroidectomy in our hospital and received a diagnosis of papillary thyroid carcinoma, were included in the study. In histopathological specimens, the diagnosis of papillary thyroid carcinoma was reconfirmed and non-neoplastic areas in the same specimen were evaluated in terms of HT.

Results. HT was detected in non-neoplastic areas of specimens in 36.1% (n = 390) of 1080 patients with a diagnosis of papillary thyroid carcinoma whereas HT was not observed in 63.9% (n = 690). There was a significant positive correlation between presence of HT and multifocal location (p < 0.05, $\chi^2 = 38.5$). There was no significant relationship between extrathyroidal tissue invasion and HT (p > 0.05).

Conclusion. We assume that patients with HT developing papillary thyroid carcinoma have an increased risk of having multifocal tumour, and thus surgical intervention should be tailored according to this risk.

KEY WORDS: Hashimoto's thyroiditis, thyroid cancer, papillary, thyroidectomy

RIASSUNTO

Obiettivo. Ci siamo proposti di indagare retrospettivamente una relazione tra tiroidite di Hashimoto e carcinoma papillare della tiroide e di studiare l'effetto della tiroidite di Hashimoto (HT) sui fattori prognostici.

Metodi. Sono stati inclusi nello studio 1080 pazienti, che sono stati sottoposti a tiroidectomia nel nostro ospedale e hanno ricevuto la diagnosi di carcinoma papillare della tiroide. Nei campioni istopatologici dei pazienti è stata riconfermata la diagnosi di carcinoma papillare della tiroide e sono state valutate le aree non neoplastiche dello stesso campione in termini di HT.

Risultati. La tiroidite di Hashimoto è stata rilevata in aree non neoplastiche dei campioni nel 36,1% (n = 390) dei pazienti con diagnosi di carcinoma papillare della tiroide mentre la tiroidite di Hashimoto non è stata osservata nel 63,9% (n = 690). L'analisi ha rivelato una correlazione statisticamente significativa tra la presenza della tiroidite di Hashimoto e la localizzazione multifocale (p < 0,05, $\chi^2 = 38,5$). Non c'era alcuna relazione statisticamente significativa tra l'invasione del tessuto extratiroideo e la tiroidite di Hashimoto (p > 0,05).

Conclusioni. Presumiamo che i pazienti con tiroidite di Hashimoto che sviluppano un carcinoma papillare della tiroide abbiano un aumentato rischio di avere un tumore multifocale, quindi, l'intervento chirurgico dovrebbe essere personalizzato in base a questo rischio.

PAROLE CHIAVE: tiroidite di Hashimoto, cancro della tiroide, papillare, tiroidectomia

Received: August 25, 2020

Accepted: December 30, 2020

Correspondence

Fatih M. Hanege

Istanbul Medeniyet University, School of Medicine, Department of Otorhinolaryngology and Head & Neck Surgery, Goztepe Training and Research Hospital, Istanbul, Turkey
Tel. +90 532 502 6239. Fax +90 216 566 6614
E-mail: hanege@hotmail.com

Funding

None.

Conflict of interest

The Authors declare no conflict of interest.

How to cite this article: Hanege FM, Tuysuz O, Celik S, et al. Hashimoto's thyroiditis in papillary thyroid carcinoma: a 22-year study. Acta Otorhinolaryngol Ital 2021;41:142-145. <https://doi.org/10.14639/0392-100X-N1081>

© Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale



OPEN ACCESS

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-Non-Commercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: <https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>

Introduction

Hashimoto's thyroiditis (HT) is a common autoimmune disorder of the thyroid gland. It can be encountered in all age groups. It is 10-20 times more common in females than in males. Although its aetiology is not fully elucidated, it is known that it is related to the release of cytokines, which damage thyroid follicle cells, following the activation of the helper T lymphocytes. Hypothyroidism is found in the majority of patients with HT¹.

HT has two major components from a histopathological point of view. The first is lymphoplasmacytic cell infiltration into stroma. In addition, histiocytes and scattered multinucleated giant cells may be also observed. The second main feature is oxyphilic changes in the epithelium paving the thyroid follicles. These cells, also called as Askanazy or Hurthle cells, have nuclei that are larger than normal, as well as prominent nucleoli and wide acidophilic and granular cytoplasm. In addition, similar to that in papillary thyroid carcinoma (PTC), cells may contain optically clear nuclei, which tend to overlap follicle epithelium. In HT, the number of the thyroid follicles decrease in parallel with increased inflammatory infiltration. Follicles with an intact appearance are usually smaller than normal and contain less colloid than normal. Limited fibrosis in the thyroid glands is observed in pathological examinations of patients with HT. However, in the fibrous variant of the disease, connective tissue constitutes more than 30% of the thyroid and this variant is encountered in 12% of all patients^{2,3}.

Following the first description of the relationship between inflammation and cancer by Virchow in 1863, the relationship of cancer with inflammation of organs such as the lung, stomach, bowel and skin has been investigated⁴. The relationship between HT and PTC was first reported by Dailey and colleagues in 1955⁵. Although this relationship was investigated in several studies, consensus has not yet been achieved⁶⁻⁹.

In this retrospective study, in which archived data of the last 22 years were screened, our objective was to investigate the presence of HT in PTC and the effect of HT on prognostic factors.

Materials and methods

The study protocol was approved by the local Ethics Committee (2017-14/24). Patient approval was not necessary because this is a retrospective study. We included 1080 patients whose pathology specimens were available for review and diagnosed with PTC who underwent thyroidectomy between 1995 and 2017 in our hospital. The examination of haematoxylin-eosin-stained histopathological materials of these patients was repeated by a single pathologist. With

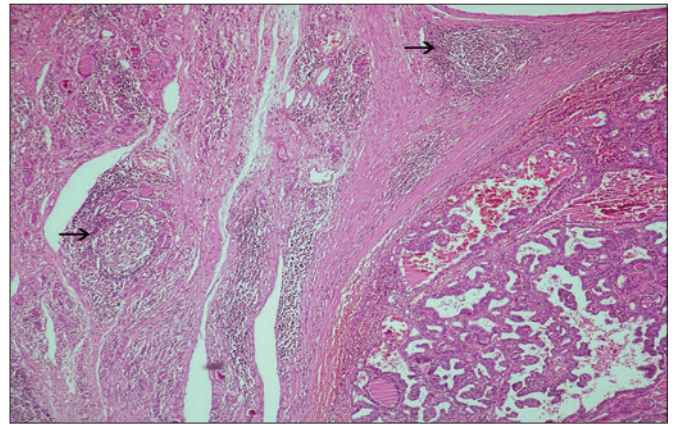


Figure 1. Lymphoid follicular and Hurthle cells surrounding the papillary carcinoma.

this examination, first the diagnosis of PTC was confirmed and secondly the non-neoplastic fields in the same specimen were evaluated for the presence of HT. Regarding HT, the presence of Hurthle cells and lymphocytic inflammation with a germinal centre in the thyroid parenchyma and stroma were the main findings looked for (Fig. 1). Moreover, tumour size, extrathyroidal tissue infiltration and multifocality in PTC fields were evaluated.

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used to evaluate data. Fisher's Exact and Chi-square tests were used to compare data. Significance was set at 0.05.

Results

57.5% of patients (n = 621) were female and 42.5% (n = 459) were male. The mean age of patients was 47 ± 14 years (23-78 years). HT was observed in non-neoplastic fields in 36.1% of 1080 patients diagnosed with PTC (n = 390). The remaining 690 patients (63.9%) had no HT findings. 56.5% of female patients with PTC (n = 351) were HT-negative and 43.5% (n = 270) were HT-positive, whereas 73.8% of males (n = 339) were evaluated as HT-negative and 26.2% (n = 120) as positive.

Of 690 HT-negative patients, 83.5% had PTC with unifocal involvement and 16.5% had multifocal PTC. On the other hand, of 390 HT-positive patients, 53% had unifocal PTC and 47% had multifocal PTC. The correlation analysis showed a significantly positive correlation between HT presence and multifocality ($p < 0.05$, $\chi^2 = 38.5$).

Evaluation of extrathyroidal tissue invasion showed that there was extrathyroidal infiltration in 13.9% of HT-positive and 16.9% of HT-negative specimens. No significant relationship was found between extrathyroidal tissue invasion and HT ($p > 0.05$).

Moreover, there was no significant relationship of HT presence with age, tumour size and lymphovascular infiltration in patients diagnosed with PTC ($p > 0.05$).

Discussion

Despite developments in surgical techniques, the underlying causes of PTC have not yet been fully elucidated. It has not been clearly demonstrated whether papillary carcinoma is a reactive response to HT or if HT is a precursor to PTC development⁸. A number of studies have been conducted to answer this question¹⁰⁻¹⁶. In the first study conducted by Dailey, the incidence of PTC in patients with HT was 35%⁵. In subsequent studies, Schäffler reported the lowest rate (8%) and Repplinger reported the highest rate (63%)^{10,17}. Matesa-Anić et al.¹¹, in their study on 10,580 subjects, which is the largest study on this topic, found an incidence of 42%. In this study, different from other studies, the rate of HT in patients with PTC was investigated and 36.1% of 360 patients with PTC had findings of HT in non-neoplastic fields. Konturek and his colleagues showed that the incidence of PTC was 3 times higher in patients with HT¹.

The relationship between HT and differentiated thyroid carcinoma was investigated in several studies and some investigators have suggested that there was an association between PTC and HT. Regarding its pathogenesis, many authors have tried to demonstrate the relationship between HT and PTC intracellular signaling proteins. In particular, phosphatidylinositol 3-kinase (PI3K), plays a critical role in the balance between cell life and apoptosis¹⁸. Cunha and colleagues found that there were different cell combinations and that CD4, CD33 and CD11b-positive lymphocytes were involved in the development of thyroid carcinoma¹⁹.

It has been reported that extrathyroidal invasion was significantly decreased in PTC patients with HT^{9,20}. In our study, evaluation of extrathyroidal tissue invasion showed that 13.9% of HT-negative patients and 16.9% of HT-positive patients had extrathyroidal infiltration. However, no significant relationship was seen between extrathyroidal tissue invasion and HT ($p > 0.05$).

Kim et al.²¹ determined that multifocal and bilateral thyroid carcinoma was more common in HT patients. Sakorafas and Falvo found similar results^{22,23}. In our study, similar to the literature, multifocal PTC was more common in patients with HT and the relationship was statistically significant.

As our study had a retrospective design, we had limited access to clinical, radiological and biochemical data. However, regarding the data we were able to obtain, the risk of developing PTC in HT patients should be taken into consideration and follow-up should be planned accordingly.

Conclusions

Biopsy of all suspected nodes will increase the probability of making the correct diagnosis in patients scheduled for fine needle aspiration biopsy. Lobectomy can be performed as an option in patients who are diagnosed with PTC and have small and single nodules. Since the risk of having multifocal disease is high in HT patients developing PTC, total thyroidectomy should be planned and a selective neck dissection should be carried out in lymph node-positive patients.

Acknowledgements

This study was presented at XI Balkan congress of ORL, Varna, Bulgaria, 31 May-3 June 2018.

References

- Konturek A, Barczyński M, Wierchowski W, et al. Coexistence of papillary thyroid cancer with Hashimoto thyroiditis. *Langenbecks Arch Surg* 2013;398:389-394. <https://doi.org/10.1007/s00423-012-1021-x>
- Berho M, Suster S. Clear nuclear changes in Hashimoto's thyroiditis. A clinicopathologic study of 12 cases. *Ann Clin Lab Sci* 1995;25:513-521.
- Ito M, Naruke Y, Mihara Y, et al. Thyroid papillary carcinoma with solid sclerosing change in IgG4-related sclerosing disease. *Pathol Int* 2011;61:589-592. <https://doi.org/10.1111/j.1440-1827.2011.02701.x>
- Guarino V, Castellone MD, Avilla E, et al. Thyroid cancer and inflammation. *Mol Cell Endocrinol* 2010;321:94-102. <https://doi.org/10.1016/j.mce.2009.10.003>
- Dailey ME, Lindsay S, Skahan R. Relation of thyroid neoplasms to Hashimoto disease of the thyroid gland. *AMA Arch Surg* 1955;70:291-297. <https://doi.org/10.1001/archsurg.1955.01270080137023>
- Ehlers M, Schott M. Hashimoto's thyroiditis and papillary thyroid cancer: are they immunologically linked? *Trends Endocrinol Metab* 2014;25:656-664. <https://doi.org/10.1016/j.tem.2014.09.001>
- Azizi G, Keller JM, Lewis M, et al. Association of Hashimoto's thyroiditis with thyroid cancer. *Endocr Relat Cancer* 2014;21:845-852. <https://doi.org/10.1530/ERC-14-0258>
- Zhang Y, Dai J, Wu T, et al. The study of the coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. *J Cancer Res Clin Oncol* 2014;140:1021-1026. <https://doi.org/10.1007/s00432-014-1629-z>
- Selek A, Cetinarslan B, Tarkun I, et al. Thyroid autoimmunity: is really associated with papillary thyroid carcinoma? *Eur Arch Otorhinolaryngol* 2017;274:1677-1681. <https://doi.org/10.1007/s00405-016-4414-6>
- Repplinger D, Bargren A, Zhang YW, et al. Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer? *J Surg Res* 2008;150:49-52. <https://doi.org/10.1016/j.jss.2007.09.020>
- Matesa-Anić, Matesa N, Dabelić N, et al. Coexistence of papillary carcinoma and Hashimoto's thyroiditis. *Acta Clin Croat* 2009;48:9-12.
- Boi F, Lai ML, Marziani B, et al. High prevalence of suspicious cytology in thyroid nodules associated with positive thyroid autoantibodies. *Eur J Endocrinol* 2005;153:637-642. <https://doi.org/10.1530/eje.1.02020>

- ¹³ Cipolla C, Sandonato L, Graceffa G, et al. Hashimoto thyroiditis coexistent with papillary thyroid carcinoma. *Am Surg* 2005;71:874-878.
- ¹⁴ Kim EY, Kim WG, Kim WB, et al. Coexistence of chronic lymphocytic thyroiditis is associated with lower recurrence rates in patients with papillary thyroid carcinoma. *Clin Endocrinol (Oxf)* 2009;71:581-586. <https://doi.org/10.1111/j.1365-2265.2009.03537.x>
- ¹⁵ Consorti F, Loponte M, Milazzo F, et al. Risk of malignancy from thyroid nodular disease as an element of clinical management of patients with Hashimoto's thyroiditis. *Eur Surg Res* 2010;45:333-337. <https://doi.org/10.1159/000320954>
- ¹⁶ Mazokopakis EE, Tzortzinis AA, Dalieraki-Ott EI, et al. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. A retrospective study. *Hormones (Athens)* 2010;9:312-317. <https://doi.org/10.14310/horm.2002.128>
- ¹⁷ Schäffler A, Palitzsch KD, Seiffarth C, et al. Coexistent thyroiditis is associated with lower tumour stage in thyroid carcinoma. *Eur J Clin Invest* 1998;28:838-844. <https://doi.org/10.1046/j.1365-2362.1998.00363.x>
- ¹⁸ Erdogmus S, Takır M, Kostek O, et al. Relationship between papillary thyroid cancer and Hashimoto's disease. *Medeniyet Med J* 2016;31:186-191.
- ¹⁹ Cunha LL, Morari EC, Guihen AC, et al. Infiltration of a mixture of immune cells may be related to good prognosis in patients with differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* 2012;77:91825. <https://doi.org/10.1111/j.1365-2265.2012.04482.x>
- ²⁰ Loh KC, Greenspan FS, Dong F, et al. Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1999;84:458-463. <https://doi.org/10.1210/jcem.84.2.5443>
- ²¹ Kim ES, Lim DJ, Baek KH, et al. Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules. *Thyroid* 2010;20:885-891. <https://doi.org/10.1089/thy.2009.0384>
- ²² Sakorafas GH, Giotakis J, Stafyla V. Papillary thyroid microcarcinoma: a surgical perspective. *Cancer Treat Rev* 2005;31:423-438. <https://doi.org/10.1016/j.ctrv.2005.04.009>
- ²³ Falvo L, D'Ercole C, Sorrenti S, et al. Papillary microcarcinoma of the thyroid gland: analysis of prognostic factors including histological subtype. *Eur J Surg Suppl* 2003;588:28-32.