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ORIGINAL ARTICLE

Is Hashimoto's thyroiditis a risk factor for medullary thyroid carcinoma? Our experience and a literature review

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Abstract The etiology of medullary thyroid carcinoma remains unknown. The aim of this study was to determine whether there is a significant association between medullary thyroid carcinoma and Hashimoto's thyroiditis in the histopathologic material of thyroidectomized patients. Retrospective cross-sectional study. In this study, we reviewed the medical records of all patients who underwent total thyroidectomy for different thyroid-related complaints between January 2000 and January 2012 at Jordan University Hospital—Amman, Jordan. To highlight relevant previously published studies addressing this topic, a literature search was conducted for English language studies reporting "medullary thyroid carcinoma" or "C-cell hyperplasia" in patients with Hashimoto's thyroiditis. Of the 863 patients with a mean age of 47.2 ± 12.3 years who underwent total thyroidectomy during the study period, 78 (9.04 %) were diagnosed with Hashimoto's thyroiditis, and 15 (1.74 %) had medullary thyroid carcinoma, 3 (20 %) of whom had coexistent Hashimoto's thyroiditis. A total of 683 (79.1 %) patients had benign thyroid disease, 67 (9.8 %) of whom had Hashimoto's thyroiditis. The difference between these rates was not statistically significant ($p = 0.19$). When examined by gender, 9 females had medullary thyroid carcinoma, 3 (33.3 %) of whom had coexistent Hashimoto's thyroiditis; by contrast, of 560 females with benign thyroid disease, 62 (11.1 %) had Hashimoto's thyroiditis ($p = 0.04$). Although this study population represents a small and single-institution experience, our results suggest that there might be an association between Hashimoto's thyroiditis and medullary

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thyroid carcinoma only in female patients who undergo total thyroidectomy.

Keywords Hashimoto's thyroiditis · Medullary thyroid carcinoma · Jordan · Thyroidectomy

Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor that arises from the C cells (parafollicular cells) of the thyroid gland. It accounts for 5–8 % of all thyroid cancers. MTC occurs in both nonhereditary (sporadic) and hereditary forms [1]. In sporadic MTC, which accounts for approximately 80 % of all disease cases, most patients already have metastases at the time of the diagnosis. Approximately 50 % of the patients have clinically detectable cervical lymph node involvement, and approximately 5 % of the patients have distant metastatic disease [1]. Thus, the prognosis depends on early diagnosis, which could be achieved through the recognition of the predisposing factors of MTC. C-cell hyperplasia (CCH) is reportedly a potential precancerous condition to MTC even in the absence of germline mutations in the rearranged during transfection (RET) proto-oncogene [2, 3]. Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism in areas of the world in which dietary iodine levels are sufficient. HT is characterized by gradual autoimmune-mediated thyroid failure with occasional goiter development [4, 5].

The association of HT with several types of thyroid neoplasia has been recognized. In patients with HT, the risk of primary thyroid lymphoma is increased by a factor of 67 [6]. Nonetheless, primary thyroid lymphoma is a rare complication of HT [5]. Additionally, the association of HT and papillary thyroid carcinoma (PTC) has been recognized in several studies [7–10]. Notably, the prognosis of PTC appears to be more favorable in patients with coexistent HT than in patients without HT [10]. The association between HT and MTC, if any, appears to be weak. Only a few reports have addressed such an association, possibly because of the distinct cell origins of these two conditions [11–18].

Because of the paucity of studies in this field worldwide, the absence of such studies in the Middle East, and the possible impact of the geographical variability and of the studied population on the development of some diseases, we conducted a retrospective cross-sectional study to investigate whether there is an association between HT and MTC in the histopathologic material of thyroidectomized patients in Jordan. To highlight relevant previously published studies addressing this topic, a literature search was conducted for English language studies reporting "MTC" or "C-cell hyperplasia" (CCH) in patients with HT.

Materials and methods

This retrospective cross-sectional study was conducted at Jordan University Hospital (JUH)—Amman, Jordan, following approval from the institutional scientific committee and the approval review board at JUH.

From January 2000 to January 2012, 863 patients underwent total thyroidectomy at JUH for different thyroid-related complaints. Of these 863 patients, 775 patients had nodular thyroid disease, which was confirmed by thyroid ultrasound examination. The remaining 88 (10.2 %) patients had diffuse Graves' disease ($n = 40$ patients) (4.6 %) or other benign diffuse goiters ($n = 48$ patients) (5.6 %). In all of the cases, a preoperative thyroid hormone assay (TSH and free T4) and thyroid ultrasound examination were performed. Only 2 patients exhibited preoperative serum calcitonin (CT) measurements that were significantly elevated (>100 pg/ml). Fine needle aspiration (FNA) was performed in 621 cases. The results of 613 FNA cases were available. The other 154 patients underwent thyroid surgery without FNA because of large goiters. The authors reviewed the clinicopathologic features of the 863 patients who underwent total thyroidectomy. The patients who underwent thyroid lobectomy, hemithyroidectomy, or excisional biopsy, including nodule excision, were excluded from this series because in patients with unilateral MTC, the evaluation of C-cell hyperplasia (CCH) requires that all blocks from the contralateral thyroid lobe be examined to exclude the possibility of overinterpretation of invasive malignancy.

The histopathologic diagnosis of HT was based on the presence of diffuse lymphocytic infiltration, oxyphilic cells, the formation of lymphoid features, and occasional reactive germinal centers. The presence of diffuse lymphocytic infiltration (DLI) alone was not considered to be HT. Positive antithyroid peroxidase antibodies (anti-TPO) were not an essential criterion for the diagnosis of HT, because histological examination represents a positive confirmation of its diagnosis. For the sake of this study, the presence of DLI and/or anti-TPO antibodies without other histopathologic features of HT was referred to as autoimmune DLI. The diagnosis of MTC was made by the presence of round, spindle-shaped, or polygonal cells with eosinophilic cytoplasm and was confirmed by positive immunohistochemical staining for CT. Because there is no consensus regarding the diagnostic criteria of CCH, the definition used in this study was the presence of ≥50 C cells in at least one low-power field (100×).

Literature search methodology and eligibility criteria

To compare the results of our study to others, we conducted a literature search. We searched PubMed, Cochrane

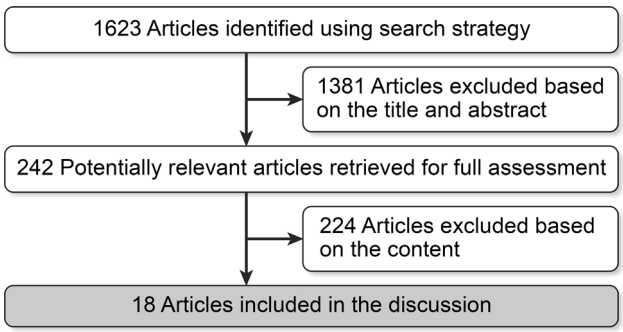

Fig. 1 Flow chart of articles included in the systematic review

Library, Web of Science, Science Direct, and SCOPUS using the following search strategy: ('hashimoto disease' OR 'chronic lymphocytic thyroiditis') AND ('medullary thyroid carcinoma' OR 'thyroid neoplasms' OR 'C-cell hyperplasia' OR 'C-cell density'). We restricted our search to publications in the 'English language' and on 'Human Subjects'. We also checked the reference sections of relevant articles for additional articles of interest. The search was performed three times and the last search was performed in January 2014 (Figure 1).

Statistical analysis

The Statistical Package for the Social Sciences, version 17.0 for windows (SPSS Inc. Chicago: SPSS Inc. USA.), was used for the analysis. Group differences were examined using the Chi-square test in the case of categorical variables and the independent sample *t* test in the case of continuous variables. Fisher's exact test was also used when the expected value in any of the cells of a contingency table was <5. The observed differences were considered to be statistically significant at $p < 0.05$.

Results

Of the 863 patients who underwent total thyroidectomy, 180 (20.86 %) had thyroid carcinoma, 15 (1.74 %) of whom had MTC. There were 137 (15.9 %) patients with PTC, 27 (3.13 %) with follicular carcinoma, and 1 (0.1 %) patient with squamous cell carcinoma. The remaining 683 (79.14 %) patients had benign thyroid disease (BTD), including HT, lymphocytic thyroiditis, granulomatous thyroiditis, benign colloid nodules, benign cystic nodules, hyperplastic nodules, multinodular goiter, follicular adenoma, and Graves' disease. The clinicopathologic features of the patients are summarized in Table 1 and are divided into nine groups by diagnosis.

For the 15 patients ($n = 9$ females, 60 %; $n = 6$ males, 40 %) in whom MTC was diagnosed, the mean age was 50.2 ± 15.1 years, whereas 560 (82 %) females and 123 (18 %) males with a mean age of 43.8 + 13.1 years were diagnosed with BTD. The differences between these two groups in terms of age were not statistically significant ($p = 0.06$) but were significant in terms of gender ($p = 0.03$). Of the 15 patients in whom MTC was diagnosed, 3 (20 %) had coexistent HT; of the 683 patients with BTD, 67 (9.8 %) had HT. The difference between these rates was not statistically significant ($p = 0.19$). When examined by gender, 9 females had MTC, 3 (33.3 %) of whom also had HT; by contrast, of 560 females with BTD, 62 (11.1 %) had HT. The difference between these rates was statistically significant ($p = 0.04$).

Additionally, 49 patients had autoimmune DLI. Of the 15 patients with MTC, none (0.00 %) had autoimmune DLI, whereas of the 683 patients with BTD, 49 (7.2 %) had autoimmune DLI. The difference between these 2 rates was not statistically significant ($p = 0.28$, OR = 0.93). Examination by gender revealed that 560 females had BTD, 37 (6.6 %) of whom also had autoimmune DLI; by contrast, none (0, 00 %) of the 9 females with MTC had autoimmune DLI ($p = 0.43$, OR = 0.93). An analysis comparing patients with HT or autoimmune DLI as one group to patients with MTC as another group revealed no statistically significant difference among all patients ($p = 0.71$, OR = 1.28) or within female gender ($p = 0.22$, OR = 2.36).

When comparing patients with MTC to those with concomitant MTC and HT, no significant difference was

Table 1 Clinicopathologic features of 863 patients with thyroid disease by diagnosis during the period 2000–2012

Diagnosis[a]	No. of cases (%)	Gender (M:F) N (%)	Mean age (years) ± SD	No. of HT (%)
BTD	683 (79.14)	123 (18 %):560 (82 %)	43.8 ± 13.1	67 (9.81)
Medullary carcinoma	15	6 (40 %):9 (60 %)	50.2 ± 15.1	3
Papillary carcinoma	137 (15.9 %)	35 (25.5 %):102 (74.5 %)	40.75 ± 12.97	8
Follicular carcinoma	27 (1.85 %)	9 (33 %):18 (67 %)	46.5 ± 15.2	0
Squamous cell carcinoma	1 (0.1 %)	1 (100 %):0 (0 %)	62	0

BTD benign thyroid disease, includes Hashimoto's thyroiditis, lymphocytic thyroiditis, granulomatous thyroiditis, benign colloid nodules, benign cystic nodules, hyperplastic nodules, multinodular goiter, and follicular adenoma, *CCH* C-cell hyperplasia

[a] No reported cases of C-cell hyperplasia, anaplastic carcinoma, thyroid lymphoma, or secondary malignancies involving the thyroid

Table 2 Clinicopathologic features of MTC patients

Characteristics	Group 1 (MTC), $n = 12$	Group 2 (MTC + HT), $n = 3$	*P* value*
Mean age (years)	49.9 ± 14.2	51.3 ± 21.7	0.9
Gender (M/F)	6/6	0/3	0.1
TSH level ≥ 4.5 mU/L	0	0	
TSH level ≤ 0.3 mU/L	0	0	
Tumor size range (cm)	1.1–3.1	1.4–2.2	0.71
Nodal involvement	7/12	2/3	0.69
Distant metastasis	0	0	

HT Hashimoto's thyroiditis; *MTC* medullary thyroid cancer; *TSH* thyroid-stimulating hormone

* *P* value < 0.05 was considered statistically significant

observed with respect to age (49.9 + 14.3 vs. 51.3 + 21.7 years; $p = 0.9$). Interestingly, all 3 patients with concomitant MTC and HT were female, whereas only 6 of the 12 patients with MTC without HT were female. Accordingly, female gender increased the risk of having both MTC and HT with an odds ratio of 2.0. Nevertheless, there was no statistically significant difference between the two groups ($p = 0.1$), likely due to the small sample size. Additionally, there were no statistically significant differences between these two groups in terms of thyroid function status, tumor size, nodal involvement, or distant metastasis (Table 2). Of note, all 3 patients with concomitant MTC and HT were seropositive for anti-TPO antibodies.

While all 15 patients with MTC underwent FNA preoperatively, MTC was diagnosed in only one patient by FNA, and the final histopathological examination confirmed the diagnosis. Of the 15 patients with MTC, only 2 had serum CT measurements. Serum CT was measured in our laboratory using a DiaSource CT-enzyme linked immunosorbent assay (ELISA) kit. In this assay, normal values are considered to be <11 pg/mL. Unfortunately, serum CT was not measured in the other 13 MTC patients preoperatively because MTC was not expected. The patient chart review of the 15 patients with MTC indicated that only one patient had flushes but denied diarrhea. The other 14 patients lacked the clinical manifestations of serum hypercalcitoninemia. None of the MTC patients in this study had a family history of MTC. Notably, a RET proto-oncogene analysis was not performed on our MTC patients. However, CCH was not diagnosed in any of the 863 patients with thyroid disease.

Of the 863 patients with thyroid disease, 78 (9.04 %) patients were found to have HT by histopathology (Table 1); 75 (96 %) of these patients were positive for anti-TPO antibodies and antithyroglobulin antibodies. Of these 78 patients, 20 had a preoperative FNA biopsy of a nodular lesion that was positive or suspicious for malignancy. The other 58 patients underwent thyroidectomy for cosmetic reasons.

Of the 78 HT patients, 3 had coexistent MTC, 8 had coexistent PTC, and 67 had coexistent BTD. When comparing patients with HT to those without HT in the BTD group, the subgroups significantly differed with respect to age and gender. Sixty-two (92.5 %) patients with HT were female, whereas 498 (80.8 %) patients without HT were female ($p = 0.02$). Additionally, patients with HT were younger than those without HT (38.9 ± 11.3 vs. 44.4 ± 13.2 years; $p = 0.001$).

Systematic literature search

The searches yielded a total of 1623 articles, of which 1380 were excluded based on the title and abstract. Thus, 242 potentially relevant articles were retrieved for full assessment (Figure 1). The articles were assessed independently

Table 3 Studies involving a link and the absence of a link between HT and MTC

Author	Year	Comments	(Ref)
Zeman/Hanika	1977	Case report of 1 patient with HT, MTC, and bilateral pheochromocytoma	[11]
Weiss et al.	1983	Case report of 1 patient with HT and MTC	[12]
Segal et al.	1985	Reported 7 cases of HT with thyroid cancer, 1 of whom had MTC	[14]
McLeod et al.	1988	Of 816 patients with thyroidectomies, 9 had MTC, 1 of whom had coexistent HT	[19]
Gaskin et al.	1992	Reported 3 cases of HT and MTC	[15]
Niccoli et al.	1997	Of 1,167 patients with thyroidectomies, 16 had MTC, 8 (50 %) of whom had mild or diffuse thyroiditis[a]	[20]
De Pasquale	2004	Case report of 1 patient with HT and MTC	[13]
Karanikas et al.	2004	Identified 1 patient with HT and MTC out of 414 referrals with thyroid disease, 55 of whom had HT	[16]
Schuetz et al.	2006	Of 568 HT patients, 1 MTC and 1 CCH were diagnosed	[17]
Papi et al.	2006	Of 1425 NTD patients screened with CT, 9 MTC patients were diagnosed, 3 of whom had chronic thyroiditis[a]	[21]
Mousa et al.	2011	Case report of 1 patient with HT and MTC	[18]

CCH C-cell hyperplasia, *CT* serum calcitonin, *HT* Hashimoto's thyroiditis, *MTC* medullary thyroid carcinoma, *NTD* nodular thyroid disease

[a] The authors did not comment on their definition of thyroiditis

Table 4 Studies involving links and/or absence of any links between CCH and HT (and/or CLT)

Author	Year	Comments	(Ref)
Libbey et al.	1989	Reported a 63-year-old man with HT and CCH	[25]
Biddinger et al.	1991	2 cases of 9 with CLT had CCH Reported a man with CLT and bilateral CCH	[26]
Guyetant et al.	1994	22 (20 %) out of 112 patients with CLT had CCH[a]	[27]
Baschieri et al.	1989	No CCH in 13 HT patients	[29]
Barbot et al.	1991	3 (12.5 %) patients out of 24 HT patients had CCH	[24]
Lukács et al.	1997	Focal and diffuse CCH was present in 16 (34.8 %) and 1 (2.2 %) out of 46 HT patients, respectively	[28]
Schuetz et al.	2006	Of 568 HT patients, 1 case of CCH was diagnosed	[17]
Gakiopoulou et al.	2010	13 (12.1 %) patients out of 107 HT patients had CCH[b]	[30]

CLT chronic lymphocytic thyroiditis; *CCH* C-Cell hyperplasia, *HT* Hashimoto thyroiditis

[a] CCH was defined as $>$ 40 C-cells/cm^2 + at least 3 LPFs containing $>$ 50 C-cells

[b] CCH was defined as $>$ 25 chromogranin positive cells/5 LPFs (X100)

by two authors. Only the articles that reported on MTC or CCH and HT were included. Accordingly, our search strategy ultimately yielded 18 publications (Table 3, 4).

Discussion

The association of HT with thyroid lymphoma and papillary thyroid carcinoma has been recognized in the literature [5–10], but few reports have discussed an association between HT and MTC (Table 3) [11–21].

The first reported case of HT associated with MTC was published in 1977 [11]. Several investigators have reported a similar association between HT and MTC, most of which were case reports [12–15, 18]. In a small study, Segal et al. reported seven cases of HT associated with different types of thyroid carcinoma [14]. Three of the cases were follicular thyroid carcinoma, two were mixed papillary and follicular carcinoma, one was anaplastic cancer, and one was MTC. In the same study, Segal et al. demonstrated that the prognosis of patients with both HT and thyroid cancer was better than that of patients with thyroid cancer alone. The authors suggested that thyroid carcinoma stimulates the development of HT in several patients and that the autoimmune inflammatory reaction retards the growth and dissemination of the carcinoma.

Consistent with the idea that HT is not a premalignant lesion to thyroid carcinoma, including MTC, another small study reported three cases of MTC coexisting with HT in patients whose relatives had multiple endocrine neoplasia type II. The authors postulated that HT occurred in response to the tumor process and not vice versa [15].

In a large study, Karanikas et al. aimed to compare the relevance of elevated CT levels in 414 referrals with neoplastic and non-neoplastic thyroid disease to 362 healthy controls [16]. Of the 414 referrals, 55 patients met the clinical diagnosis of HT.

Whenever serum CT exceeded 10 pg/ml, a pentagastrin stimulation test was performed. Although none of the healthy controls had an abnormal pentagastrin stimulation test, four of the referral patients exhibited abnormal test results. Only one of the four had a final histopathological diagnosis of MTC. Thus, the prevalence of MTC was 0.24 % (1/414) in the entire referral group and 1.8 % (1/55) in the HT group [16]. In another large study, serum CT was measured in 568 consecutive patients with HT to evaluate the frequency and relevance of elevated CT in these patients. When the serum CT was $\geq$10 pg/ml, a pentagastrin stimulation test was performed. Only two patients with abnormal tests were identified, one with MTC and one with CCH and PTC [17]. Accordingly, the prevalence of MTC in HT was only 0.18 %.

Our data demonstrated no significant difference between the prevalence of HT in patients with MTC (20 %) compared with those with BTD (9.8 %) ($p = 0.19$). Nevertheless, when examined by gender, there was a statistically significant association between HT and MTC in females only. Among the females studied, 3 of 9 (33.3 %) patients with MTC had coexistent HT, whereas 62 of 560 (11.1 %) patients with BTD had HT ($p = 0.04$). Nevertheless, it is important to remember that there was no statistically significant association between MTC and autoimmune DLI alone, and no significant association was observed between MTC and all patients with autoimmune DLI or HT. The significant association between HT and MTC exclusively in females should be considered cautiously because of the following factors: (a) our series included a limited number of patients with MTC (only 15), nine of whom were females; (b) HT is more common in females; and (c) it is unclear whether such an association between HT and MTC in females is coincidental or whether there is a pathogenic relationship between the two diseases. Additionally, in the latter case, it is not clear whether HT predisposes a person to MTC or whether HT is a defense against the neoplasm.

Another important limitation of this study is that it represents only a single-institution experience.

Thus, it will be necessary to study a larger number of patients with MTC to determine its association with HT and to prospectively follow large populations of patients with and without HT to assess the development of CCH and MTC before this issue can be resolved. The lack of any significant association between MTC and HT in most studies could be attributed to the distinct cell origins of these two conditions. Another factor to consider is the rarity of MTC, which accounts for only 5–8 % of all thyroid cancers [22]. Studies from the Mayo Clinic have suggested that the incidence of thyroid cancer, including small occult tumors, is approximately 60 per million cases per year [23]. Accordingly, the incidence of MTC would be approximately 3–4.8 per million cases per year. Of note, over a 57-year period (1940–1997), only 218 patients with MTC were treated at the Mayo Clinic [5]. Thus, it is possible that the lack of a statistically significant association between these two conditions in most studies could be related to the small sample size of patients with MTC.

Because neoplastic CCH is considered a precursor of MTC, the understanding of the pathological link between CCH and HT may help scientists to understand the pathophysiological link between MTC and HT [2, 3]. Table 4 summarizes the studies that have reported the presence or absence of an association between HT and CCH [17, 24–30]. In 1989, the first case of CCH associated with HT was reported [25]. Similarly, in a study of 24 patients with HT, Barbot et al. reported 3 patients with CCH [24]. In a retrospective surgical material study of 112 chronic lymphocytic thyroiditis (CLT) patients, 20 % of the patients had CCH, defined as a C-cell density of >40 cells/cm^2 and the presence of at least three LPFs containing >50 C cells [27]. Recently, in another study, CCH defined as >25 chromogranin-positive cells/5 LPFs (×100) was not observed in any of the 20 patients with nodular hyperplasia [30]. In contrast, CCH was detected in 13 (12.1 %) patients with HT and in 2 (6.8 %) patients with Graves' disease [30].

Our study did not reveal CCH in any of the patients with or without HT. This finding is in agreement with the data of Baschieri et al., who reported that none of their 13 patients with HT had CCH [29]. Similarly, a low prevalence of CCH (0.18 %) in patients with HT was reported in a study by Schuetz et al. [17].; of 568 HT patients screened by serum CT measurements, only 1 patient was diagnosed with CCH.

Notably, diagnosing CCH is difficult because there is no consensus regarding its diagnostic criteria [3]. Thus, different definitions of CCH were used in different trials. Although the CCH definition that we used was among the least strict, no cases of CCH were reported. This observation is unusual given that one patient (at the age of 51) in our series was clinically considered to have MEN2a but did not exhibit underlying CCH. Because this study was retrospective and the status of RET germline mutations was unknown, the study pathologist reviewed all of the slides from patients with MTC to exclude possible errors in the diagnosis. However, no CCH was detected.

Two types of CCH have been identified: neoplastic CCH (also called MTC in situ) and physiologic (also called reactive) CCH [31, 32]. Neoplastic CCH is thought to be the precursor of hereditary MTC and, most likely, sporadic MTC, even in the absence of germline RET mutations [3, 31, 33]. Physiologic CCH is believed to be caused by external stimuli to the C cell, including inflammatory, neoplastic, and metabolic disorders [3, 31, 33]. In contrast to neoplastic CCH, the premalignant potential of physiologic CCH is not documented [31, 33].

Is the CCH associated with HT physiologic or neoplastic? This is a critical question with no clear answer. Several investigators have reported that CCH associated with HT may involve an immune reaction that is elicited by cytokines and inflammatory mediators secreted by infiltrating lymphocytes in HT [16, 30, 34]. In support of this hypothesis, a recent study reported that CCH was not encountered in any patients with nodular hyperplasia but was present in 12.1 % of patients with HT and 6.8 % of patients with Grave's disease [30]. The possibility of a C-cell growth factor that is over-expressed in hyperplastic C cells adjacent to follicular cells has also been suggested [27, 35]. Unfortunately, these hypotheses do not differentiate between physiologic or neoplastic HT-associated CCH. Based on cytological atypia in neoplastic C cells, CCH associated with HT has been hypothesized to reflect a physiologic response of C cells rather than a neoplastic response [31]. However, this hypothesis has been debated because the morphology of both neoplastic and physiologic C cells can be extremely variable [2, 36, 37]. CCH associated with HT could be purely fortuitous, given that the C-cell density in normal patients exhibits significant variability and that up to 20 % of normal individuals may have CCH [34, 38]. Moreover, there is some evidence that CCH could be an age-related phenomenon with a dramatic male predominance [30, 39–41].

In this respect, it is unclear whether the association among females in our study sample between MTC and HT is fortuitous or pathogenic. Thus, studying a larger number of patients with MTC to verify such an association is warranted.

Of note, the prevalence of MTC among patients with thyroid disease in our study reached 1.74 %, which is higher than that previously published in a series of more than 100 patients, in which the incidence of MTC ranged from 0.24 to 1.37 % [16, 20]. The composite prevalence of MTC is 0.31 % across 15,992 patients from 12 series [42].

The reason for this high prevalence has not been established. Consanguineous marriage, which is common in Jordan, could contribute to this high prevalence. We believe it would be interesting to evaluate the prevalence of MTC in other Middle Eastern countries that have similar environmental and cultural backgrounds, including consanguineous marriages. To the best of our knowledge, such data are not available.

In conclusion, despite the obvious and inherent limitations of this study, our results suggest that there might be an association between HT and MTC only in female patients who undergo total thyroidectomy. Larger prospective studies are required to confirm these findings.

In addition, our study indicates that the prevalence of MTC in patients with thyroid disease is higher than previously reported in published series from other regions. Although consanguineous marriage could contribute to this high prevalence, the reasons for this elevated prevalence remain unclear.

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