Incidental papillary thyroid microcarcinoma in consecutive patients undergoing thyroid surgery for benign disease.

A single center experience.

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Incidental papillary thyroid microcarcinoma in consecutive patients undergoing thyroid surgery for benign disease. A single center experience.

BACKGROUND: *There has recently been an increase in the incidental histological diagnosis of papillary thyroid microcarcinoma (I-PTMC), that varies from 3.5% in autopsies studies, to 5.2% in thyroid specimens from thyroid surgery, up to 9.4% in patients from areas of endemic goiter.*
AIM: *To evaluate the incidence and the histological characteristics of I-PTMC in patients undergoing thyroidectomy for benign thyroid diseases, and to evaluate sex, age, toxic and non-toxic goiter, Hashimoto's thyroiditis as potential risk factors.*
MATERIALS AND METHODS: *Prospective observational study on 124 patients, median age 56.3±13.25sd range 24-80 years, 93(75%)F, 31(25%)M, with surgical indications for toxic and non-toxic uni/multinodular goiters, in pharmacological euthyroidism. An accurate histological examination (HE) of entirely embedding thyroid samples was performed to identify microscopic foci of I-PTCM. Logistic regression analysis of the abovementioned parameters was performed to identify the risk factors.*
RESULTS: *Total incidence of I-PTMC was 15.3%(19/124), with F/M ratio 2:1. All I-PTMCs were intraparenchymal with an intact thyroid capsule; 68.5% were bilateral-multifocal, 21% unilateral-unifocal, 10.5% unilateral-multifocal; maximum diameter was <5mm in 57.9% and ≥5mm in 42.1%; 63.1% were follicular variant, 36.9% classical variant; intra-thyroid lymphatic invasion and lymph node infiltration of the central compartment and para-tracheal was found in the only patient with "tall-cell" classical variant. No risk factors was found.*
CONCLUSIONS: *The incidence higher than that reported in the literature, is probably due to the accurate HE of entirely embedding thyroid samples, which is the most important tool to identify microscopic foci of I-PTCM. The highest reported rate of bilateral multifocality of the neoplasm recommend the total thyroidectomy as surgical treatment of choice, also in patients undergoing thyroid surgery for "presumptive" benign diseases.*

KEY WORDS: Benign Thyroid Disease, Incidental Papillary Thyroid Microcarcinoma, I-PTCM, Thyroid Surgery

Introduction

According to the World Health Organization (WHO), the papillary thyroid microcarcinoma (PTMC) has a diameter of ≤1.0 cm at the time of the hystological diagnosis [1-3]. Histologically two varieties of PTMC, the unifocal and the multifocal, are known [4]. Multifocality, bilateralism, capsule invasion and lymph node metastases are considered predictors of high biological aggressiveness [5,6].

The preoperative diagnosis of PTMC is generally difficult, based on routine ultrasonography (US), the US elastography, the CT and the fine needle aspiration citology (FNAC) [7,8]. Preoperative evaluation of the anti-thy-

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roid autoantibodies and thyroglobulin has not been proven to be helpful in the diagnosis [8].

PTMC can occur with three different presentations according to the method of detection: a) clinical diagnosis, for vocal cord paralysis, lymph node metastases or distant metastases from an occult PTMC [9]; b) US diagnosis, by the discovery of non-palpable small tumors; c) incidental PTCM (I-PTCM), an incidental histological diagnosis after total thyroidectomy (TT) or after a completion of the preceding hemithyroidectomy.

Despite the invasion of the thyroid capsule is reported in 5.4% of incidental papillary thyroid microcarcinoma [10], generally the I-PTMC is characterized by a low morbidity, low mortality and favorable prognosis [11]. In recent years, there has been a significant increase in the diagnosis of the I-PTMC. The reported histological incidence of I-PTMC is 3.5% in autopsies studies and 5.2% in thyroid specimens obtained from thyroid surgery; the incidence increases up to 9.4% in patients from areas of endemic goiter [10,12-14].

Gender and age are not statistically correlated to the incidence of the neoplasm [15], although Hashimoto's chronic lymphocytic thyroiditis appears to be associated with a significant increase of PTMC risk especially in young adults [15-17].

The main purpose of this study is to evaluate the incidence and the histological characteristics of I-PTMC, in a series of consecutive patients undergoing thyroid surgery for benign diseases.

The secondary purpose consists on the evaluation of the correlation between sex, age, toxic and non-toxic goiter, Hashimoto's thyroiditis and I-PTMC.

Material and Methods

Prospective observational study, performed in accordance with the principles of the Helsinki Declaration, conducted at the hospital "A. Fiorini" of Terracina, UOC Surgery University, Faculty of Pharmacy and Surgery-Polo Pontino, University of Rome "La Sapienza".

Patients (pts) undergoing a TT or a completion previous thyroid surgery for benign disease, between January 2018 and February 2021, were enrolled in the study.

The study included the following criteria of exclusion: pre-operative diagnosis of malignant thyroid disease, age <18 years old (yo) and > 85 yo, ASA score >3, pregnancy and breastfeeding, neurological and psychiatric disorders with impaired ability to understand, refusal to sign informed consent.

In all the cases surgical indication was recommended by the endocrinological experts, and was represented by the non toxic uni/multi nodular goiters (non-toxic NG) and toxic uni/multi nodular goiters (toxic NG), the latters diagnosed as clinical or subclinical hyperthyroidism and lesions with scintigraphic signs of functional autonomy, in pharmacological euthyroidism.

Every surgical procedure was performed by the same team of experts in thyroid surgery.

An accurate histological examination (HE) of entirely embedding thyroid samples was performed by the same histologists, to identify microscopic (<5 mm) foci of papillary carcinoma. The neoplasm was staged according to the 8th Edition UICC/AJCC TNM classification.

The following demographic, clinical, and histopathological parameters were evaluated:

age, sex, indication to surgery, surgical procedure type adopted, multifocality, bilaterality and dimensions (≥/<5 mm) of the I-PTMC, histotype according to WHO 2017, invasion of the thyroid capsule, angio-lymphatic invasion, lymph node metastases, findings of Hashimoto's thyroiditis.

The data were collected and processed through IBM SPSS v.23.0 software. The comparison between the collected data was conducted using logistic regression analysis, with a statistical significance set at $p < 0.05$.

Results

The study included 124 pts, with median age 56.3yo, sd±13.25 yo, range 24-80 yo; 93 (75%) Female (F), with median age 56.3 yo, sd±13.5 yo, range 24-80 yo, and 31 (25%) Male (M) with median age 56.5 yo, sd±12.48 yo, range 30-75 yo. TT was performed in 120/124 (96.8%) pts and completion of previous hemithyroidectomy in 4/124 (3.2%) pts. Non-toxic NG was the most common indication of the surgical treatment with 97 (78.2%) pts. In 27 (21.8%) pts the surgical procedure was performed for toxic NG. In reported I-PTMC the

Table I - *Demographic and Clinical features of the sample.*

Features	Total sample 124 patients n. (%)
Age (years)	
Median ±sd	56.3 ±13.2
Range	24-80
Sex	
Female	93 (75)
Male	31 (25)
Surgical indication	
Non-toxic NG	97 (78.2)
Toxic NG	27 (21.8)
ASA score	
I	20 (16.1)
II	91 (73.4)
III	13 (10.5)
Surgical procedure	
TT	120 (96.8)
Completion	4 (3.2)

sd = standard deviation; NG = nodular goiter; TT = total thyroidectomy

Table II - *I-PTMC: histopatological features of the 19 cases.*

Histopatological Findings	I-PTMC 19 patients n. (%)
Histopatological variant	
Follicular	12 (63.1)
Classic	7 (36.8)*
Dimensions	
<5 mm	11 (57.9)
≥5mm	8 (42.1)*
Localisation	
Bilateral Multifocal	13 (68.5)*
Monolateral Monofocal	4 (21)
Monolateral Multifocal	2 (10.5)
Thyroid capsule invasion	
Yes	0
No	19 (100)
Intra-thyroid lymphatic invasion	
Yes	1 (5.2)*
No	18 (94.8)
Lymph-node metastasis	
Yes	1 (5.2)*
No	18 (94.8)

*one patient with "tall cell" classical variant

patients were subjected to TT for non-toxic NG in 16 (84.2%) and for toxic NG in 3 (15.7%) cases.
Demographic and Clinical features of the sample are shown in Table I.
The total incidence on the examined sample of I-PTMC was of 15.3% (19/124 pts), with median age 53.7 yo, sd±12.6 yo, range 24-80 yo; of which 6 M (31.57%) with median age 51.2 yo, sd±6.8 yo, range 45-64 yo, and 13 F (68.42%) with median age 55 yo, sd±14.7 yo, range 24-80 yo.
I-PTMCs resulted in bilateral multifocal in 13/19 (68.5%) pts, unilateral unifocal in 4/19 (21%) pts, unilateral multifocal in 2/19 (10.5%) pts. The maximum diameter of the lesion was of <5mm in 11/19 (57.9%) pts, ≥5mm in 8/19 (42.1%) pts. The follicular variant of PTMC was diagnosed in 12/19 (63.1%) pts, and classical variant in 7/19 (36.9%)pts. Only in one patient of 62 yo, with "tall cell" classical variant, the immunohistochemical stains for CD31 and CD34 showed intrathyroid lymphatic invasion, and was found neoplastic infiltration in two lymph nodes of the central compartment (CC) and 1 right para-tracheal lhymp node. In all the cases the lesion was intraparenchymal, with an intact thyroid capsule.
The histological characteristics of I-PTMC are shown in Table II. Histopatological Hashimoto's thyroiditis was diagnosed in 5/19 (26.3%) pts with I-PTCM, 1 patient of 24 yo and 4 pts of age > 30 yo, and in 27/105 (25.7%) pts without I-PTCM.
Sex, age, toxic and non-toxic NG, and Hashimoto's disease did not statistically significantly correlate with incidence of I-PTMC, not configuring as a risk factor.
The logistic regression results are shown in Table III.

Discussion

The significant increase of I-PTMC, observed in the last 20 years in the general population, should be kept in mind in clinical practice because it influences the therapeutic strategy [18].
After each TT and completion of previous emithyroidectomy carried out for "presumptive" benign thyroid disease, an accurate HE is indicated because the PTMC is not always recognized in the traditional US investigation, nor in the FNAC exam [18].
In our study the incidence of I-PTMC in the sample examined was 15.3%, significantly higher than the data reported in the literature [12,18]. Without the accurate examination of the entire thyroid samples embedded for routine histology, the real incidence of I-PTCM in our study would probably has been underestimated.

Table III - *Risk factors of I-PTCM (logistic regression analysis results).*

Risk Factors	I-PTMC 19 pts (15.3%) n. (%)	Non I-PTCM 105 pts (84.6%) n. (%)	P*
Age (years)			
Median ±sd	53.7 ±12.6	56.8 ±13.3	0.355
Range	24-80	30-78	
Sex			
Female	13 (68.42)	80 (76.1)	0.471
Male	6 (31.57)	25 (23.8)	
Surgical indication			
Non-toxic NG	16 (84.2)	81 (77.1)	0.468
Toxic NG	3 (15.7)	24 (22.8)	
Hashimoto's thyroiditis	5 (26.3)	27 (25.7)	0.836

* statistical significance set at p <0.05; sd = standard deviation; NG = nodular goiter

Moreover, unlike what is described in the literature in which multifocality and bilaterality were respectively 23.3% and 13.3%, in our study the 19 cases of I-PTMCs described were bilateral multifocal in 68.5%, monofocal and monolateral in 21%, and unilateral multifocal 10.5% [5,18]. Our data prove that entirely embedding thyroid samples is the most important tool for identifying microscopic foci, clinically inapparent, of papillary carcinoma.

Furthermore, in our study the histological diagnosis of I-PTMC was associated with the presence of factors of greater biological aggressiveness of the neoplasm: bilateral multifocality in 13 pts and lymph node involvement in one patient with the "tall cell" variant. So we recommend a careful exploration of the CC in the course of TT, for a possible albeit infrequent lymph node involvement in the I-PTMC.

The papillary carcinoma with "tall cell" aspects occurs more often in elderly patients and present itself with large size, infiltrative growth pattern, and extra-thyroid extension to the diagnosis [19]. In accordance with what is reported in the literature, our patient with I-PTCM with "tall cell" aspects was older than the average age of the sample, and neoplasia showed greater histological aggressiveness, which manifested itself with a bilateral extension, a maximum diameter of 9 mm, an intra-thyroid lymphatic invasion, lymph node envolvement of the CC and invasion of the right para-tracheal lymph node.

About the malignancy risk assessment of toxic goiter in our study there is no significative difference in the incidence of malignancy between toxic NG and non-toxic NG, but as a recent systematic review has highlight further research are need [20].

Although in our study sex, age and Hashimoto's disease did not significant statistically correlate with the incidence of I-PTMC, not configuring as a risk factor, they showed some differences with respect to the literature.

The opposite to what is reported in the literature, were the I-PTMC are more frequently found in M rather than in F with a 3:1 ratio [21], in our experience it was more frequently diagnosed in F rather than in M with 2:1 ratio. Unlike what is reported in literature, where incidental neoplastic lesions are diagnosed in all ages, in our study the young adults were found to have a very low incidence of I-PTMC [17]. In fact in the age group of 18-30 yo I-PTCM was found in only one patient of 24 yo. It is hypothesized that Hashimoto's autoimmune thyroiditis is responsible for the initiation of the neoplastic process favoring the expression of some proto-oncogenes [16], and it is considered a risk factor for PTMC especially in young adults [17]. In our study Hashimoto's thyroiditis in I-PTCM has been identified in the only young patient of 24 yo and in 4 pts with age >30 yo. The narrowness of the sample examined, with consequent limited statistical power, does not allow us to define with a level of certainty the existence of a correlation between Hashimoto's thyroiditis and I-PTMC.

As reported in literature, in the case of I-PTMC, TT alone is associated with a favorable prognosis with survival at 5 years >98% [22-24]. According to our experience, when surgical management is recommended for "presuntive" benign thyroid disease, it requires the extension of the indications to TT as surgical treatment of choice, followed by an accurate histological examination of entirely embedding thyroid samples, in all cases. Adjuvant nuclear treatment in the majority of patients was found to be unnecessary and, in our experience, it was reserved for patients with the "tall cell" variant, whose biological aggressiveness is known [10].

Conclusion

We believe that therapeutic strategies for thyroid nodules should be planned taking into consideration also the high incidence of I-PTMC, as observed in our study in pts undergoing surgical treatment for benign thyroid disease.

However larger prospective studies, with accurate histological examination of entirely embedding thyroid samples, are needed to validate the results obtained.

Riassunto

SCOPO: Recentemente è stato riscontrato un aumento della diagnosi istologica incidentale del microcarcinoma papillare della tiroide (I-PTMC). L'incidenza istologica varia dal 3.5% negli studi autoptici, al 5.2% negli esami dei campioni operatori da chirurgia tiroidea, fino al 9.4% nei pazienti provenienti da aree di gozzo endemico. Lo scopo principale di questo studio è stato quello di valutare l'incidenza e le caratteristiche istologiche dell'I-PTMC nei pazienti con indicazione alla chirurgia tiroidea per patologia benigna della tiroide. Obiettivo secondario è stato quello di valutare le caratteristiche demografiche, cliniche e istopatologiche (sesso, età, gozzo tossico e non tossico, tiroidite di Hashimoto) quali potenziali fattori di rischio di I-PTCM.

PAZIENTI E METODI: Studio prospettico osservazionale eseguito su 124 pazienti, 93(75%) F, 31(25%) M, con età mediana 56.3±13.25sd, range 24-80 anni, sottoposti a chirurgia tiroidea tra Gennaio 2018 - Febbraio 2021, con indicazione posta dagli specialisti endocrinologi per patologia benigna, quale gozzo uni/multinodulare, non tossico e tossico, in eutiroidismo farmacologico. Per ciascun paziente è stato eseguito un accurato esame istologico di tutta la tiroide, aumentando i campionamenti al fine di identificare i focolai microscopici di I-PTCM. È stata eseguita l'analisi di regressione logistica dei suddetti parametri demografici, clinici e istopatologici, allo scopo di identificarli quali eventuali fattori di rischio.

RISULTATI: L'incidenza totale di I-PTMC è stata del 15.3% (19/124), con rapporto F/M 2:1. Tutti gli I-

PTMC erano intra parenchimali con capsula tiroidea intatta; il 68.5% era bilaterale-multifocale, il 21% unilaterale-unifocale, il 10.5% unilaterale-multifocale; il diametro massimo era <5mm nel 57.9% e ≥5 mm nel 42.1%; il 63.1% era una variante follicolare, il 36.9% una variante papillare classica; l'invasione linfatica intratiroidea e l'infiltrazione linfonodale del comparto centrale e para-tracheale è stata riscontrata nell'unico paziente con variante classica "tall-cell". Sesso, età, gozzo tossico e non tossico, tiroidite di Hashimoto non si sono configurati come fattori di rischio.

CONCLUSIONI: Nel nostro studio l'incidenza di I-PTCM significativamente superiore a quella riportata in letteratura, è probabilmente dovuta all'accurato esame istopatologico eseguito includendo tutta la tiroide e aumentando il numero dei campionamenti, che è lo strumento più importante per identificare i focolai microscopici di I-PTCM. Il più alto tasso di multifocalità bilaterale della neoplasia, riscontrato nella nostra esperienza, raccomanda la tiroidectomia totale come trattamento chirurgico di scelta, anche nei pazienti sottoposti a chirurgia tiroidea per patologia "presunta" benigna.

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