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Original Article / Оригинални рад

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Incidence and morphological features of thyroid papillary microcarcinoma in Graves' disease

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SUMMARY

Introduction/Objective Association of Graves' disease (GD) and thyroid cancer is reported in a wide range from 0% to 33.7%. Papillary thyroid carcinoma (PTC) is the most commonly diagnosed malignancy in GD, namely its variant papillary thyroid microcarcinoma (PTMC). The increasingly frequent PTMC disclose favorable biological behavior with low mortality and recurrency rates.

Objective The aim of this work is to report our experience on frequency and morphological features of PTMC in surgically treated patients with GD.

Materials and methods In three years period total or near-total thyroidectomy was performed in 129 patients with GD.

Results Incidental PTMC was diagnosed in 24 (18.7%) patients with GD . The mean tumor diameter was 3.03±2,17mm. The average age of patients in the group GD with PTMC was 48.50 ± 13.07 years old, while in the group GD without PTMC was 41±13.12 years old, and it proved to be statistically significant (p = 0.045). Most of the PTMC were unifocal (83%), and the most common morphological features of PTMC were: intraparenchymal localization (62.5%), follicular morphology (66.7%) and infiltrative growth pattern (62.5%). Extrathyroid extension, lymphatic invasion and multifocality of PTMC were more commonly related with subcapsular localized PTMC. The presence of at least one nodules in the group GD with PTMC was 58.3%, while in the group GD without PTMC was 26.7%, and it was statistically significant (p=0.003).

Conclusion Our results showed a high incidence of PTMC (18.7%) in patients with GD. Clinically, the most important morphological characteristics of PTMC were related with its subcapsular localization.

Keywords Grave's disease; thyroid papillary microcarcinoma; morphology

САЖЕТАК

Увод/Циљ Удруженост Грејвсове болести (ГБ) и карцинома штитасте жлезде пријављује се у широком распону до 0% до 33,7%. Папиларни карцином (ПК) штитасте жлезде је најчешћи малигнитет у ГБ, односно његова варијанта папиларни микрокарцином (ПМК). Упркос сталном порасту учесталости ПМК, његова стопа рецидива и смртности је константна и ниска.

Циљ рада је да се одреди учесталост и морфолошке карактеристике ПМК код болесника са ГБ и тиреоидектомијама.

Методе У периоду од јануара 2013. године до децембра 2015. анализирани су општи клинички и морфолошки параметри код 129 болесника са ГБ и учињеном тоталном или скоро тоталном тиреоидектомијом.

Резултати Код 24 (18,7%) болесника са ГБ дијагностикован је ПМК. Пречник тумора износио је 3,03±2,17mm (0,45–7mm). Старост болесника у групи са ГБ и ПМК износила је 48,50±13,07 година, а у групи без ПМК 41±13,12 година и била је статистички значајна (p=0,045). Микроскопски, најзаступљенији параметри били су: само један фокус ПМК (83,3%), фоликуларни подтип ПМК (66,7%), ифилтративна форма раста (62,5%), интрапаренхимска локализација (54,2%). Присуство најмање једног нодуса у штитастој жлезди детектовано је код 26,7% болесника са ГБ без ПМК, док је у групи са ПМК било више (58,3%) и статистички високо значајно (p=0,003).

Закључак Висока је учесталост **к**арцинома штитасте жлезде код болесника са ГБ и износи 18,7%. Његове клинички најзначајније морфолошке карактеристике везане су за субкапсуларну локацију тумора.

Кључне речи Грејвсова болест; штитаста жлезда; папиларни микрокарцином; морфологија

INTRODUCTION

Graves' disease (GD) is an organ-specific autoimmune disease of thyroid gland that occurs in the presence of autoantibodies to TSH receptor, leading to gland hyperfunction, hyperproduction of hormones (thyroxine, triiodothyronine) and development of a specific clinical presentation [1]. Macroscopically, thyroid gland is usually diffusely enlarged and the histological picture is characterized by follicular hyperplasia with intraluminal/follicular infolding, occasionally in form of papillary proliferation. Thyroid gland lobularity and vascularisation are increased and it is possible to

detect a patchy lymphoid infiltration (LI) in stroma. In long-standing medically treated Grave's disease, nodular transformation of the adenomatous type can be detected, as well as development of different degrees of fibrosis, cellular atypia and oncocytic cell transformation [2, 3]. Association of GD and thyroid carcinoma is well documented with frequencies ranging from 0% to 33.7% [4-8]. The most common malignancy in reported studies of GD is papillary carcinoma (PTC), namely its variant papillary microcarcinoma (PTMC) – defined as incidentaly discovered PTC with size less or equal to 10 mm [9]. The increasingly frequent PTMC disclose favorable biological behavior with low mortality and recurrency rates [10-12].

The malignant potential of well differentiated thyroid carcinomas of follicular origine in GD is still contradictory. Some studies suggest that immunological basis of GD which is characterized by permanent autoantibody stimulation of gland epithelial and tumor cells, as well as presence of antiapoptotic Il-4 and Il-10, could affect the growth, survival and biological behavior of thyroid carcinomas [6, 13-15].

The aim of this work is to report our experience on frequency and morphological features of PTMC in surgically treated patients with GD.

METHODS

From January 2013 till December 2015 in the Clinic for Endocrine and General Surgery at Military Medical Academy in Belgrade, a total or near-total thyroidectomy was performed in 129 patients. General epidemic and clinical data (gender, age, type of surgery) were obtained from medical history of patients. Indication for surgery in 125 patients was medically uncontrolled thyroid hyperfunction, compressive symptoms, nodular presence or esthetic reason. In 4 patients, indication for thyroidectomy was a clinical suspicion for PTC, after fine-needle aspiration biopsy was performed. Macroscopic processing of surgical specimen was done according to guidelines for handling surgical specimen from Rosai and Ackerman's Surgical Pathology [2]. Scar lesion – fibrose and/or calcified foci were fully processed. Diagnosis of PTMC was done according to the classification of World Health Organisation [9]. The following morphological features of PTMC were analyzed: size, multifocality, localization, histomorphology (classical, follicular, tall cell), growth pattern (infiltrative vs. circumscribed), extrathyroid extension, lymphovascular invasion and lymph node metastasis. According to the localization PTMC were divided into those localized in to peripheral or subcapsular/superficial zone according to the criteria applied by Niemeier et al. and the PTMC localized deep into thyroid parenchym [16]. The study of remaining non neoplastic thyroid tissue included the search for nodular transformation and abundance and frequency of LI. We defined nodular transformation as presence of at least one nodule in the gland (adenomatoid, colloid, oncocytic). Abundance and frequency of LI is graded by the scale 0 – 4 according to Williams and Doniach [17]. In cases were we incidentally discovered lymph nodes in peri isthmic or peri thyroid tissue, they were fully processed and examined for the presence of metastasis.

Review of all cases was done by two pathologists (SC, BK). Cases where there was a different opinion in diagnosis of PTMC and four cases of PTC with preoperative suspicion for malignancy were excluded from the series.

Data are presented as mean ± standard deviation or count (percents), depending on data type. Significant differences between groups were assessed using t test, Mann-Whitney U test and Chi-square test, depending on data type and distribution. Data were analyzed using SPSS 20.0 (IBM corp.) statistical software. All *p* values less than 0.05 were considered significant.

RESULTS

In the analyzed period, a total of 125 patients with GD without previous suspicion of a malignancy were surgically treated. After histopathological examination diagnosis of PTMC was made in 24 (19.2%) patients, with a mean tumor size of 3.03±2,17mm (0,45–7mm). The mean weight of the gland in the group GD with PTMC was 37±40.90 g, and in the group of GD without PTMC was 54.94±43.64 g. Statistical significance was not determined according to weight of the gland (Z= -0.940, p = 0.347). One hundred and one (80.8%) patients were female, while 24 (19.2%) patients were male. Eighteen of the patients who had PTMC were female, whereas 6 were male, and there was no statistically significant difference ($\chi 2$=0.644, p=0.564). The average age of patients in the group GD with PTMC at the time of surgery was 48.50 ± 13.07 years old, while in the group GD without PTMC was 41± 3.12 years old, and it proved to be statistically significant (t=2.023, p=0.045). Clinical and pathological characteristics of the patients are shown in Table 1.

Table 1. Clinical and pathological characteristics of the patients.

	TOTAL	GD without PTMC	GD with PTMC	*p* value
Patient number	125	101	24	
GENDER				
Female	101(80.8%)	83(82.2%)	18(17.8%)	**0.564**[a]
Male	24(19.2%)	18(75%)	6(25%)	
Age(years)	44.27±13.28	43.09±13.12	49.13±13.07	**0.045**[b]
Thyroid weight (g)	53.95±43.02	54.94±43.64	49.80±40.90	**0.347**[c]
NODULAR PRESENCE				
Without Nodular transformation	84(67.2%)	74(73.3%)	10(41.7%)	
With Nodular transformation	41(32.8%)	27(26.7%)	14(58.3%)	**0.003**[a]
LYMPHOID INFILTRATION				
Grade 0	35 (28.0%)	30(29.70%)	5(20.8%)	
Grade I	80 (64%)	65(64.36%)	15(62.5%)	
Grade II	10(8.0%)	6(5.94%)	4(16.7%)	**0.129**[d]
Grade III	0 (0%)	0 (0%)	0(0%)	
Grade IV	0(0%)	0 (0%)	0 (0%)	

Legend *p*-values: a–Chi-square test, b–*t*-test, c–Mann-Whitney *U*-test, d–Chi square test for trend.

PTMC characteristics

Most of the PTMC were unifocal (n=20; 83%), and multifocality was detected in only 4 cases (n=4; 16.2%). The most common localization of PTMC was intraparenchymal (n=15; 62.5%), two of them were located in the isthmic region, while the subcapsular localization was detected in 9 cases

(n=9; 37.5%), respectively. Follicular morphology of the tumor was the most common (n=16; 66.7%), followed the classical (n=5; 20%) and tall-cell morphology (n= 3; 12.5%), respectively. Infiltrative growth pattern was found in 15 cases (n=15; 62.5%) compared to the circumscribed cases (n=9; 37.5%). Lymphatic invasion was present in 4 cases (n=4; 16.7%), and vascular invasion was not seen in none of the cases. Extrathyroid microscopic extension was detected in 3 of 24 cases (12.5%) and it was related to subcapsular localization of PTMC. Subcapsular PTMC were also more commonly related with morphological features such as multifocality and lymphatic invasion. Three of 4 cases with lymphatic invasion and all cases with multifocal distribution were subcapsular PTMC. In twelve cases of the group GD with PTMC, one to 5 lymph nodes were found. In none of these cases lymph node metastasis were found. The pathomorphological characteristics of the PTMC of all patients are shown in Table 2. Figures 1A–D shows several histomorphological findings.

Table 2. Pathomorphological characteristics of the PTMC for all patients.

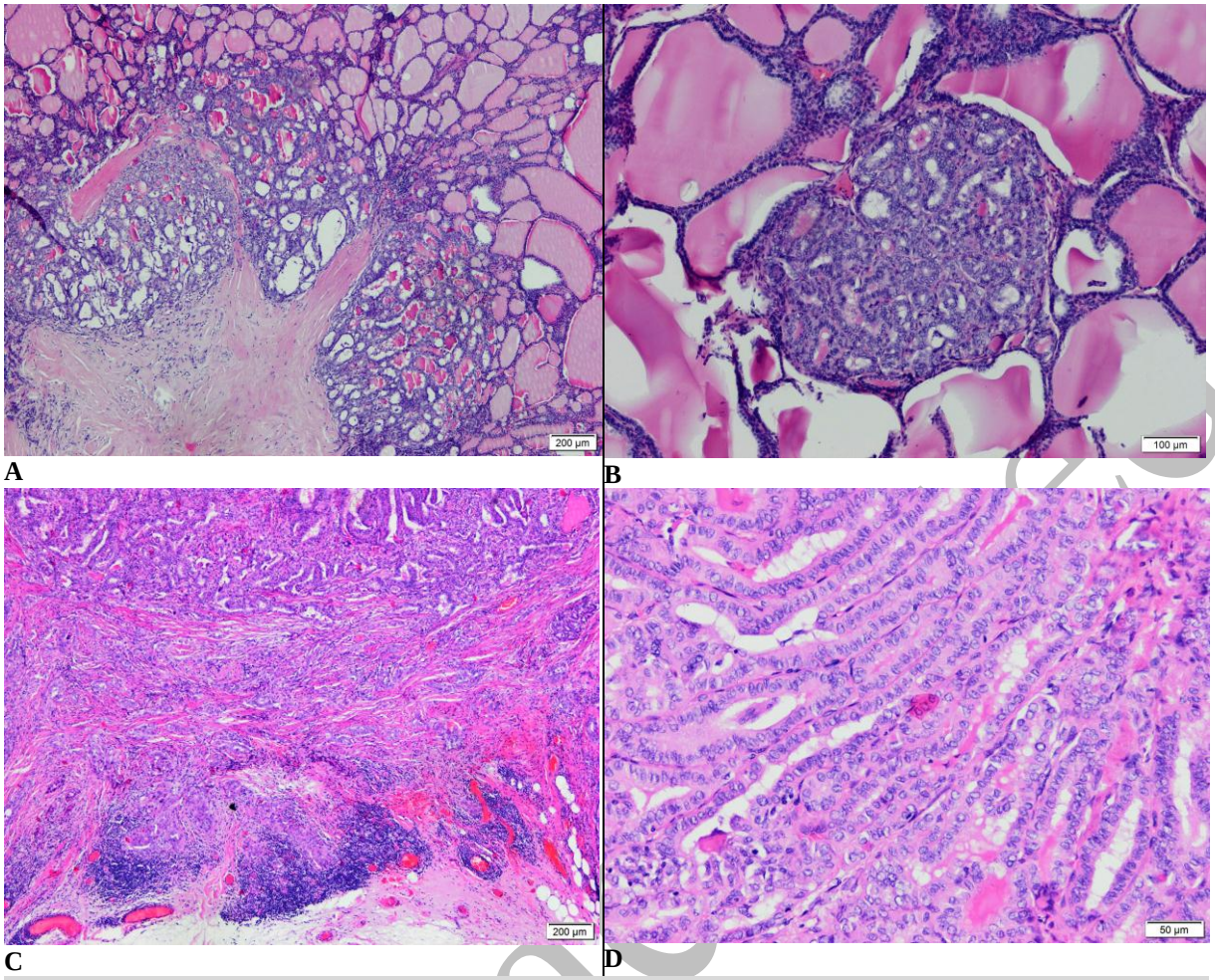
Case	Age (yrs)	Sex	Size (mm)	TNM	Localization	Morphology	GP	Multifocality	LV
1	35	M	0.9	T1aNx	IP	Fol.	Circ.	No	L0V0
2	73	M	0.9	T1aNx	SC	Fol.	Inf.	No	L0V0
3	46	F	4	T1aN0(0/2)	IP	Fol.	Inf.	No	L0V0
4	56	F	4	T1aNx	IP	Fol.	Inf.	No	L0V0
5	48	F	3.9	T1aN0(0/4)	IP	Fol.	Inf.	No	L1V0
6	58	M	1.8	T1aNx	IP	Fol.	Circ.	No	L0V0
7	63	F	1.35	T1aNx	IP	Clas.	Inf.	No	L0V0
8	63	F	2.4	T1aNx	IP	Fol.	Inf.	No	L0V0
9	33	F	2.4	T1aN0(0/4)	IP	Clas.	Inf.	No	L0V0
10	47	F	7	T3Nx	SC	Tall	Inf.	No	L1V0
11	49	F	5	T1aN0(0/2)	IP	Fol.	Circ.	No	L0V0
12	46	M	3.3	T1aN0(0/3)	SC	Fol.	Circ.	Yes	L0V0
13	25	F	7	T3Nx	SC	Clas.	Inf.	No	L1V0
14	60	F	1.95	T1aNx	IP	Clas.	Inf.	No	L0V0
15	53	F	6	T1aNx	IP	Clas.	Circ.	No	L0V0
16	36	F	2	T1aNx	SC	Fol.	Inf.	No	L0V0
17	58	F	6	T1aNx	IP	Fol.	Inf.	No	L0V0
18	64	M	1.2	T1aN0(0/1)	SC	Fol.	Circ.	No	L0V0
19	47	F	1.5	T1aN0(0/2)	SC	Tall	Inf.	Yes	L0V0
20	41	M	0.9	T1aN0(0/2)	IP(Ist.)	Fol.	Circ.	No	L0V0
21	24	F	1.35	T1aN0(0/3)	IP	Fol.	Circ.	No	L0V0
22	65	F	2	T1aNx	SC	Fol.	Inf.	Yes	L0V0
23	35	F	0.45	T1aN0(0/1)	IP(Ist.)	Fol.	Circ.	No	L0V0
24	54	F	7	T3N0(0/5)	SC	Tall	Inf.	Yes	L1V0

GP- growth pattern; LV- lymphovascular invasion; IP- intraparenchymal; SC- subcapsular; Ist. Isthmic; Fol.- follicular morphology; Clas.- classical morphology ; Tall cell morphology; Inf- infiltrativ growth; Circ.- circumscribed.

Additional findings in GD in relation to PTMC

Nodular presence

The nodular presence was detected in 41 of 125 (32.8%) cases. In 5 cases (12%) nodules were solitary, with diameter ranging form 7 mm to 25 mm. Three of them were of adenomatous type and one was of colloid type. In 36 cases (82%) nodules were multiple with diameter ranging from 2 mm to 30 mm. The morphology of these nodules was mixed of hyperplastic/adenomatous and/or of colloidal type. Presence of oncocytic nodules was detected in three cases. The presence of nodules in the group



A **B** **C** **D**

Figure 1. A- Follicular PTMC with infiltrative growth pattern (H&E, ×40). B- Submillimetre size circumscribed PTMC (H&E, ×100). C- Subcapsular PTMC with extrathyroid extension (H&E, ×40). D – Tall cell PTMC (H&E, ×200).

GD with diagnosed PTMC was found in 14 of 24 cases or 58.3%, while in the group GD without PTMC the presence of nodules was found in 27 of 101 or 26.7%, and it proved to be statistically significant ($\chi 2$= 8.786; p= 0.003).

Presence of lymphoid infiltration

In the total group of analyzed patients the most prevalent presence of lymphoid infiltration was within Grade I. Grade I of LI was detected in 84 of 125 cases or 64%, followed Grade 0 and Grade II with 28% and 8% of cases. In the group of GD with PTMC results were very similar: Grade 0 of LI was present in 5 of 24 cases or 20.8%, Grade I of LI was present in 15 of 24 cases or 62.5%, followed Grade II in 4 of 24 cases or 16.7%. Grade III and IV of LI, which would correspond to lymphocytic or Hashimoto's thyroiditis, respectively, according to the applied criteria, were not detected in any case. PTMC was the most commonly detected within Grade I but we did not prove it to be statistically significant (p=0.129).

DISCUSSION

Reported presence of malignancy in GD is very different, but in two recent studies its frequency is very high, with rate of 32% and 33.7% [8, 18]. Increase of cancer incidence in GD is well presented in a study reported by Phitayakorn et al. [19]. This study involves a time interval of 25 years divided into three periods. In the first stated period (1985-1993) frequency of carcinoma was 0%, while in the third period (2003-2010) frequency of carcinoma was 16.4%. In a cohort study reported by Chen et al. [20] patients with GD, particularly in older age are at risk of development of thyroid carcinoma compared with general population.

The most common malignancy in GD is a PTC, with the participation of its variants PTMC from 23% to 88.0% [5,6,18,21,22]. Our results show a high incidence of malignancy in surgicaly treated patients with GD 21.7% (28/129) with high participation of PTMC (24/28)85.7%. Incidence of PTMC in patients with GD is 18.7% (24/129). The frequency of PTMC in GD was statistically significantly higher (p=0.045**)** in older patients of our series, similar by to the results of other studies [19, 21, 22]. These results are in accordance with general trend of worldwide increasing incidence of PTMC, most often as early clinical detection or as incidental pathohistological finding in patients undergoing thyroid surgery for benign thyroid lesion [10-12].

Thyroid nodules in GD are common finding and its prevalence is different depending on the detection method: thyroid palpation, ultrasonography or pathohistological examination. Using of thyroid ultrasonography as the most sensitive method, thyroid nodules are found in 28.5–53.0% of patients with GD [18, 23, 24]. Relation of thyroid nodules and carcinoma in GD is already established in a number of studies and increases the risk for developing thyroid carcinoma [5,18,21-24]. Carcinoma can be localized within nodules or into thyroid parenchyma outside nodules, most often as an incidental PTMC. In our work the presence of thyroid nodules was detected in 32.8% what is similar by to the results of 33.6% reported by Tam et al. [22] and 39% reported by Ergin et al. [21]. Frequency of PTMC was statistically significantly higher in thyroid glands with present nodules as opposed to the gland without present nodules, which is consistent with results of previous studies [5, 18, 21-24]. This results is also opposite to the study by Wei et al. who reported higher incidence of PTMC in GD without nodules [18]. Localization of PTMC in our work was outside of detected nodules except in two cases. This could be result of larger number of analyzed slides in case of nodular presence, usually in order to assess its invasive growth.

The presence of lymphoid infiltrate in the thyroid glands of GD is usually small, most often in the form of patchy and small group of lymphocytes, usually in interfollicular stroma, and sometimes with germinal center formation. Foci of LI were accompanied by secondary changes in thyrocyte, usually in the form of its degeneration and rarely oncocytic transformation [1-3, 25]. According to the medical records in our work, a clinical significance of moderate amount of LI was in association with medically uncontrolled thyroid hyperfunction. That could be an expected finding, because intrathyroid

lymphocytes are one of the main sources of autoantibodies [1]. Also, presence of the LI can lead to the follicular destruction and incresed hormone release. Abundance and frequency of LI in our work were not statistically significantly associated with presence of PTMC. Interpretation of secondary changes related to presence of LI, development of fibrosis and cellular atypia is problematic because it could be associated with therapy-induced changes, especially in the long-standing and medically treated disease, which was not subject of this analysis [2, 3].

In addition to the differences in the reporting cancer frequency in GD, opinions and results about its malignant potential are also disparate. Study Pellegriti et al. [13]. shows that well differentiate thyroid cancers in GD have a more aggressive biological behavior, which is, according to Ozaki et al. [26] also applicable to tumors lesser than 10 mm. Other studies, however, show that there are no differences in the biological behavior of cancer in the GD according to other pathological conditions [27] and prognosis of PTMC is excellent [6, 13, 28].

Usually, clinical behavior of PTMC is favorable with excellent outcome. In rare cases PTMC can show aggressive behavior presented by local lymph node metastases, extratyroid invasion or local recurrence, while a distant metastasis and fatal outcome are extremely rare [29]. Potentially different biological behavior of PTMC can be related to patients age, specifically in children and younger adolescents up to 19 years. Clinical presentations and behavior of PTMC is mostly related to its morphological features such as tumor size, its multifocality, infiltrative growth, lymphovascular invasion, histological type, and its localization [10, 30]. According to Niemeier et al. most specific and sensitive assessment of aggressiveness of PTMC is obtained by applying the combined molecular-pathological score [16].

Clinical impact of morphological characteristics of PTMC in our work were related to their peripheral/subcapsular localization. Only PTMC within this localization are able to infiltrate thyroid capsule and can show extrathyroid extension which was in our work present in 12,5%. Other features (multifocality, limphatic invasion), related to potentially more agressive biological behavior of PTMC, were also more commonly associated with subcapsular PTMC. Another important morphological characteristic of PTMC in our results was high frequency of PTMC with tall cell morphology, detected in 12,5% of cases. Tall cell variant is a clinically more aggressive form of PTC with reported incidence from 4% to 12% [30]. In recent studies, Boutizios et al. [8] represented higher incidence of tall cell variant of PTC (18%) in patiens with GD, and Wei et al. [18] reported incidence of PTC with tall cell morphology in 16% (7% were tall cell variant and 9% of PTC showed tall cell features). These results indicate that tall cell morphology as a pure PTC variant or as a part of PTC with tall cell features could be more common finding in patients with GD than in euthyroid patients. It is also interesting that all cases of PTMC with tall cell morphology in our work were in subcapsular localization.

More precise results could be expected in larger series, which is a main flaw and limitation of our present work.

Pathohistological diagnosis of PTMC is rarely problematic, but from a practical standpoint it is important to emphasize that differentially diagnostic lesions can be mostly seen in GD. Foci of papillary proliferations can be problematic, specially the ones localized in vicinity of fibrotic area with the picture of pseudoinvasion. Small hypercellular and often pseudo-encapsulated nodule with nucleomegaly and some degree of hypochromasia could be a diagnostic challenge. The most significant differential diagnostic issue represents stellate fibrotic foci as solitary or multifocal findings. In these cases the definite diagnosis usually requires serial section examination in order to assess invasive growth and/or detection of more typical PTC nuclear features or psamoma body.

CONCLUSION

Thyroid carcinoma in GD are not rare, and in our results, most of them represent an incidental PTMC. Clinical impact of PTMC is mostly related with its morphological features and tumor localization. Reporting of these features and long-term follow-up could help a better understanding of true biological nature of PTMC in GD.

REFERENCES

1. Weetman AP. Graves' disease. N Engl J Med. 2000; 343(17): 1236–48.
2. Rosai J. Rosai and Ackerman's Surgical Pathology. 10th ed. London: Elsevier Mosby; 2011.
3. Thompson LD, Goldblum JR. Head and neck pathology. Churchill Livingstone: Elsevier; 2012.
4. Rieger R, Pimpl W, Money S, Rettenbacher L, Galvan G. Hyperthyroidism and concurrent thyroid malignancies. Surgery. 1989; 106(1): 6–10.
5. Staniforth JU, Erdirimanne S, Eslick GD. Thyroid carcinoma in Graves' disease: A meta-analysis. Int J Surg. 2016; 27: 118–25.
6. Pazaitou-Panayiotou K, Michalakis K, Paschke R. Thyroid cancer in patients with hyperthyroidism. Horm Metab Res. 2012; 44(4): 255–62.
7. Slijepcevic N, Zivaljevic V, Marinkovic J, Sipetic S, Diklic A, Paunovic I. Retrospective evaluation of the incidental finding of 403 papillary thyroid microcarcinomas in 2466 patients undergoing thyroid surgery for presumed benign thyroid disease. BMC Cancer. 2015; 30; 15: 330.
8. Boutzios G, Vasileiadis I, Zapanti E, Charitoudis G, Karakostas E, Ieromonachou P, et al. Higher Incidence of Tall Cell Variant of Papillary Thyroid Carcinoma in Graves' Disease. Thyroid. 2014; 24(2): 347–54.
9. DeLellis RA, Lloyd RV, Heitz PU, Eng C. World Health Organization classification of tumors. Pathology and genetics of tumors of endocrine organs. Lyon: IARC; 2004.
10. Soares P, Celestino R, Gaspar da Rocha A, Sobrinho-Simões M. Papillary thyroid microcarcinoma: how to diagnose and manage this epidemic? Int J Surg Pathol. 2014; 22(2): 113–9.
11. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"—screening and overdiagnosis. N Engl J Med. 2014; 371(19): 1765–7.
12. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013; 2013: 965212.
13. Pellegriti G, Mannarino C, Russo M, Terranova R, Marturano I, Vigneri R, et al. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab. 2013; 98(3): 1014–21.
14. Mazzaferri EL. Thyroid cancer and Graves' disease [editorial]. J Clin Endocrinol Metab. 1990; 70: 826–9.
15. Vella V, Mineo R, Frasca F, Mazzon E, Pandini G, Vigneri R, et al. Interleukin-4 stimulates papillary thyroid cancer cell survival: implications in patients with thyroid cancer and concomitant Graves' disease. J Clin Endocrinol Metab. 2004; 89: 2880–9.
16. Niemeier LA, Kuffner Akatsu H, Song C, Carty SE, Hodak SP, Yip L, et al.k. A combined molecular-pathologic score improves risk stratification of thyroid papillary microcarcinoma. Cancer. 2012; 118: 2069–77.
17. Williams ED, Doniach I. The post-mortem incidence of focal thyroiditis. J Pathol Bacteriol. 1962; 83: 255–64.

18. Wei S, Baloch ZW, LiVolsi VA. Thyroid carcinoma in patients with Graves' disease: an institutional experience. Endocr Pathol. 2015; 26(1): 48–53.
19. Phitayakorn R, Morales-Garcia D, Wanderer J, Lubitz CC, Gaz RD, Stephen AE, et al. Surgery for Graves' disease: a 25-year perspective. Am J Surg. 2013; 206(5): 669–73.
20. Chen YK, Lin CL, Chang YJ, Cheng FT, Peng CL, Sung FC, et al. Cancer risk in patients with Graves' disease: a nationwide cohort study. Thyroid. 2013; 23(7): 879–84.
21. Ergin AB, Saralaya S, Olansky L. Incidental papillary thyroid carcinoma: clinical characteristics and prognostic factors among patients with Graves' disease and euthyroid goiter, Cleveland Clinic experience. Am J Otolaryngol. 2014; 35(6): 784–90.
22. Tam AA, Kaya C, Kılıç FB, Ersoy R, Çakır B. Thyroid nodules and thyroid cancer in Graves' disease. Arq Bras Endocrinol Metabol. 2014; 58(9): 933–8.
23. Kim WB, Han SM, Kim TY, Nam-Goong IS, Gong G, Lee HK, et al.Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. Clin Endocrinol (Oxf). 200460(6): 719–25.
24. Belfiore A, Russo D, Vigneri R, Filetti S. Graves' disease, thyroid nodules and thyroid cancer. Clin Endocrinol (Oxf). 2001; 55: 711–8.
25. LiVolsi VA. The pathology of autoimmune thyroid disease: a review. Thyroid. 1994; 4(3):333–9. [DOI: 10.1089/thy.1994.4.333] [PMID: 7833672]
26. Ozaki O, Ito K, Kobayashi K, Toshima K, Iwasaki H, Yashiro T. Thyroid Carcinoma in Graves' Disease. World J Surg. 1990; 14: 437–41.
27. Yano Y, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K, et al. Recent outcome of Graves' disease patients with papillary thyroid cancer. Eur J Endocrinol. 2007; 157(3): 325–9.
28. Kikuchi S, Noguchi S, Yamashita H, Uchino S, Kawamoto H. Prognosis of small thyroid cancer in patients with Graves' disease. Br J Surg. 2006; 93: 434–9.
29. Piana S, Ragazzi M, Tallini G, de Biase D, Ciarrocchi A, Frasoldati A, et al. Papillary thyroid microcarcinoma with fatal outcome: evidence of tumor progression in lymph node metastases: report of 3 cases, with morphological and molecular analysis. Hum Pathol. 2013; 44(4): 556–65.
30. Kuo EJ, Goffredo P, Sosa JA, Roman SA. Aggressive variants of papillary thyroid microcarcinoma are associated with extrathyroidal spread and lymph-node metastases: a population-level analysis. Thyroid. 2013; 23(10): 1305–11.

