The Assessment of Prognostic Histopathological Parameters Depending on Histological Patterns of Papillary Thyroid Carcinoma

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ABSTRACT: Papillary thyroid carcinoma represents common injuries that can have different histological variants that may influence the patient's prognostic. The study included a total of 44 papillary thyroid carcinomas, for which were followed a series of histological factors of aggressiveness for grading tumors. Most studied papillary carcinomas corresponded to the conventional type, followed by the follicular, micropapillary and tall cell variants. Depending on the presence of nuclear atypia, tumor necrosis, the frequency of mitosis, also the vascular invasion and the extrathyroidian extension there were distributions differences of the cases according to the tumor type, most of the cases belonged to the conventional and tall cell types. The assessment of histopathological parameters of aggressiveness with certain types known to have an unfavorable behavior, justify the use of the histological grading of papillary thyroid carcinomas.

KEY WORDS: papillary thyroid carcinoma, histological grade, tumor type

Introduction

Papillary carcinoma is a well-differentiated malignant tumor developed from the thyroid follicular cells, which shows a series of characteristic nuclear changes and in even witch the growth pattern is frequently papillary, it is not required for the diagnosis [1].

Papillary thyroid carcinoma (PTC) represents 1% of all malignancies [2] and about 70-80% of all thyroid cancer [3]. The incidence of thyroid carcinoma types is quite different in various studies [4-7]. In a study, conventional papillary carcinoma was 46% of the carcinomas, followed by the micropapillary carcinoma with 27.8%, by follicular variant (17.6%), tall cell variant (4%) and the diffuse sclerosing variant (1.8%), rarely been noticed the variants: solid, diffuse follicular, papillary carcinoma with focal insular component, columnar cells, necrotising-like stroma and oncocytic one.

Differentiated tumors, papillary and follicular, are mostly treatable and curable. Most of the patients with PTC have good prognosis and long-term survival in cases without distant metastases. Though, have been reported different histological patterns that may influence these patients prognostic.

In this study we followed some histological factors of aggressiveness for grading tumors and the association with the different variants of papillary carcinomas.

Material and Methods

The current study included a total of 44 papillary thyroid carcinomas from patients hospitalized and operated in Surgery Clinics of Emergency County Hospital of Craiova, in the period 2008-2012. The surgical pieces were fixed in 10% buffered formalin, processed by the usual technique with paraffin embedding and Hematoxylin-Eosin stain. Classification of the tumors was made in accordance with literature data. Tumors subclassification has been made considering that must contain at least 75% (arbitrary cutoff value) of the tumor composition of a given tumor type before being detected as specific sub-type and the variant follicular it must be 100% [8, 9].

For all investigated cases we were interested in a series of histological features as: presence/absence of nuclear atypia, presence/absence tumor necrosis, mitotic frequency on 10 areas with 40x microscopic field (MF), presence/absence of vascular invasion, presence/absence of capsular invasion and the presence/absence of extrathyroidian extension.

The histological grade of the examined tumors was defined as a summary of this histological features, grade 1(G1) was recorded when none of the histological features were
present and grade 2 (G2) was recorded when one or more of these features were present.

Parameters recorded were stored in an electronic database and statistically analyzed using SPSS 10 automatic software by using chi-square test, which analyzed the dependence between the classifications factors, values below 0.05 being considered significant.

Results

The analysis of the 44 studied papillary thyroid carcinomas noticed that most of investigated papillary carcinomas corresponded to the papillary conventional type with 25 cases (56.8%), followed by the follicular variant in 11 cases (25%), micro papillary carcinomas in 5 cases (11.4%) and the tall cell variant in 3 cases (6.8%).

The analysis of histopathological parameters of aggressiveness (Table 1) indicated only for the tall cell variant of papillary carcinomas the association in all cases with the presence of aggressiveness markers. The three papillary carcinomas, tall cell variant presented in all cases necrosis (Fig.1A), nuclear atypia and mitosis, more frequently than the rest of the tumors (3-4 mitosis on 10 areas/ 40x MF), and also vascular invasion (Fig.1B), capsular invasion (Fig.1C) and extrathyroidian in the tracheal muscle.

In contrast, papillary microcarcinomas and most of the follicular variant of papillary carcinomas didn’t associated these features. For the follicular variant of papillary carcinomas we observed the absence of nuclear atypia, of tumor necrosis and the vascular invasion. However we found for 5 cases the capsular invasion and in one case even the extrathyroidian one (Fig.1D) but the mitosis were 1-2 on 10 areas/40x MF.

In case of conventional papillary carcinomas we noticed the nuclear atypia (Fig.1E) in 5 cases, focal necrosis in 2 cases and in 3 cases 3-4 mitosis on 10 areas/40x MF (Fig.1F). Vascular
invasion was noticed in 4 cases, capsular invasion in 6 cases and extrathyroidian extension in 4 cases.

In relation with the differentiation degree, papillary micro carcinomas, conventional papillary carcinomas and the follicular variant present tumoral degree 1 in most of the cases (100%, 68% respective 54,5%), while all the tall cell carcinomas have degree 2, aspects which were statistical significant (p<0,05, chi square test) (Table 1).

Table 1. Cases distribution in relation to the analyzed histopathological parameters and tumor type

| Parameters/Tumoral type | Conventional | Micro papillary | Follicular | Tall cell variant | P value |
|-------------------------|--------------|-----------------|------------|-------------------|---------|
| nuclear atypia          | absence      | 20              | 5          | 11                | 0       |
|                         | presence     | 5               | 0          | 0                 | 3       |
| tumoral necrosis        | absence      | 23              | 5          | 11                | 0       |
|                         | presence     | 2               | 0          | 0                 | 3       |
| mitotic frequency <2    | 22           | 5               | 11         | 1                 | 0,011   |
|                         | >2           | 3               | 0          | 0                 | 2       |
| vascular invasion       | absence      | 21              | 5          | 11                | 0       |
|                         | presence     | 4               | 0          | 0                 | 3       |
| capsular invasion       | absence      | 19              | 5          | 6                 | 0       |
|                         | presence     | 6               | 0          | 5                 | 3       |
| extrathyroidian extension | absence   | 21              | 5          | 10                | 0       |
|                         | presence     | 4               | 0          | 1                 | 3       |
| histological degree G1  | 17           | 5               | 6          | 0                 | 0,003   |
| G2                      | 8            | 0               | 5          | 3                 |         |

The statistical analysis of the cases distribution regarding the tumor type and the histopathological parameters of interest, indicated significant differences (table 1). Thus, in relation with the presence of nuclear atypia, tumor necrosis, mitosis frequency, and also the vascular invasion and the extrathyroidian extension there were differences of distribution according to the tumor type, most of the cases being the conventional papillary type and the tall cell variant (p<0,05, chi square test) (Fig.2).

![Fig.2. Graphic distribution of the cases in relation with the classification factors](image)

Regarding the follicular variant of papillary carcinomas a small number of cases associated the extrathyroidian extension, capsular invasion being more frequent (p<0,05, chi square test).

Discussions

In the current study involving 44 papillary thyroid carcinomas more than half were
conventional type (56,8%), followed in order of frequency by the follicular variant in quarter of cases (25%), more rare being the papillary micro carcinomas (11,4%) and the tall cell carcinomas (6,8%). The papillary carcinomas subclassification may be difficult in most of cases with more than one architectural type or cellular patterns, tumors should have at least 75% of tumor component of a certain type before they were classified as a specific subtype and for the follicular variant is practically 100%. [8, 9] The patients with papillary carcinomas have the best surviving rate from all types of thyroid cancers, with a 10 year rate up to 95% [10] or by other studies the survival at 5 years is 96% and at 10 years of 93% [11]. Though, these values can be modified depending on other prognostic factors. Pathological variables associated with poor prognostic include the presence of less differentiated or solid areas, vascular invasion and aneuploid cell population [8, 12-15]. These features are well known as aggressiveness factors in most of the malignant tumors and can be evaluated independent of growth pattern and the tumor cells type [8], which may be an advantage in the cases in which the subclassification is difficult because of the complex and heterogeneous tumors structure. Some authors recommend that for all papillary carcinomas to be given a histological grade based on the combined examination of nuclear atypia, tumor necrosis and vascular invasion [8]. It is believed that at least four subtypes of papillary carcinomas should be considered with unfavorable prognosis: tall cell variant, diffuse sclerosing variant, solid variant and follicular variant [16].

All tall cell papillary carcinomas were associated with the aggressiveness factors, the 3 cases corresponding to grade 2. The local recurrences and the tracheal invasion are not rare, the last one complication being fatal sometimes [16]. In a recent study, 278 patients with tall cell variant of papillary carcinoma had a higher rate of extrathyroidian extension (53,6% vs 30,2%, p=0,0001) and lower specific survival with no disease at 5 years (81,9% vs. 97,8%, p=0,0001) compared to 2522 patients with conventional papillary carcinoma [17].

Conventional carcinomas corresponded in 8 cases to grade 2 (32%), being associated with nuclear atypia (5 cases), tumor necrosis (2 cases), and presence of 3 mitosis on 10 ares/40x MF (3 cases), vascular invasion (4 cases), capsular invasion (6 cases) and extrathyroidian extension (4 cases). Even if the papillary thyroid carcinomas prognostic is in generally good, some tumors are more aggressive, their evolution being related with some histopathological features.

The classification of these features in 2 risk groups indicated in some studies that patients with high-grade tumors present 50% death risk through thyroid cancer after 15 years, compared to only 5% for patients with low-grade tumors. We identified nuclear atypia in 8 cases (18,1%) of investigated papillary carcinomas, of which 5 cases were the conventional type and 3 cases tall cell variant, aspects that were statistically significant (p<0,05, chi square test). The nuclear atypia was recognized as an important prognostic factor for papillary carcinomas [18], and the marked nuclear atypia can be associated with DNA aneuploidy.

In our study, vascular invasion was noticed in all tall cell variant of papillary carcinomas, in 6 cases of follicular variant (54,5%) and in 5 cases of conventional variant (20%) (p<0,05). Identification of the tumor vascular invasion it is an aggressiveness sign, because it leads to hematogenous invasion, distant metastasis, and therefore unfavorable prognosis [19]. For the differentiated thyroid carcinomas it was found that intra or extrathyroidian vascular extension goes to local recidives and distant metastasis, more frequent in papillary carcinomas [20].

Extrathyroidian extension of tumors was identified behind tracheal wall, at the muscular tunic, in all tall cell papillary carcinomas, in 4 cases of conventional carcinomas (16%) and in one case of follicular variant of papillary carcinomas (9,1%), which was statistically significant (p<0,05, chi square test). Tumor extension beyond the thyroid capsular is in generally associated with unfavorable prognosis and some studies, by multivariate analysis, indicated that as a negative prognostic factor [21].

Conclusions
The association of histopathological parameters of aggressiveness with certain variants known to have an unfavorable behavior, justifies the useful of the histological grading of papillary thyroid carcinomas.

References
1. Nikiforov Y, Biddinger PW, Thompson LDR, Diagnostic Pathology and Molecular Genetics of the Thyroid, 1st Edition, Ed Lippincott Williams & Wilkins, Philadelphia 2009
2. Kukora JS, Thyroid cancer, in Current Surgical Treatment, Cameron JL (eds), Ed. Mosby, St.Luis, 2001, pp. 583-9
3. DeLellis RA, Lloyd RV, Heitz PU, Eng C (eds). Pathology and genetics of tumours of endocrine organs. In: Kleihues P, Sobrin LH, series editors, World health organization, Classification of Tumours, Lyon, IARC Press, 2004
4. Lam AKY, Lo CY, Lam KSL. Papillary carcinoma of thyroid: a 30-yr clinicopathological review of the histological variants. Endocr Pathol 2005; 16:323-30
5. Koo JS, Hong S, Park CS. Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. Thyroid 2009; 19:1225-31
6. Ito Y, Hirokawa M, Uruno T, Kihara M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A. Prevalence and biological behaviour of variants of papillary thyroid carcinoma: experience at a single institute. Pathology 2008; 40:617-22
7. Rufini V, Salvatori M, Fadda G, Pinnarelli L, Castaldi P, Maussier ML, Galli G. Thyroid carcinomas with a variable insular component: prognostic significance of histopathologic patterns. Cancer 2007; 110:1209-17
8. Akslen LA, LiVolsi VA. Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. Cancer 2000; 88:1902-8
9. Duntas L, Grab-Duntas Brigitte Maria. Risk and prognostic factors for differentiated thyroid cancer. Hell J Nucl Med 2006; 9:156-62
10. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994; 97:418-28
11. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer 1998; 83:2638-48
12. Akslen LA. Prognostic importance of histologic grading in papillary thyroid carcinoma. Cancer 1993; 72:260-5
13. Rosai J, Carcangiu ML, DeLeilis RA (eds). Atlas of tumor pathology. Tumors of the thyroid gland. Series 3. Fascicle 5. Washington, DC: Armed Forces Institute of Pathology, 1992
14. Baloch Z, LiVolsi VA. Pathology of the thyroid gland. In: LiVolsi VA, Asa S (eds). Endocrine Pathology. Churchill Livingstone: Philadelphia, PA, 2002, pp. 61-88
15. Moreno-Egea A, Rodriguez-Gonzalez JM, Solapervez J, Soria-Cogollos T, Parrilla-Paricio P. Multivariate analysis of histopathological features as prognostic factors in patients with papillary thyroid carcinoma. Br J Surg 1995; 82:1092-5
16. LiVolsi VA. Papillary thyroid carcinoma: an update. Modern Pathology 2011; 24: S1-9
17. Morris LG, Shahar AR, Tuttle RM, Sikora AG, Ganly I. Tall-cell variant of papillary thyroid carcinoma: a matched-pair analysis of survival. Thyroid 2010; 20:153-8
18. Mai KT, Yazdi HM, Perkins DG, Commons AS, Thomas J. Papillary thyroid carcinoma and related thyroid neoplastic lesions: a light microscopic study with emphasis on nuclear changes. Tumori 2000; 86:238-49
19. Falvo L, Catania A, D'Andrea V, Marzuolo A, Giustiniani MC, De Antoni E. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. Ann Surg 2005; 241:640-6
20. Gardner RE, Tuttle RM, Burman KD, Haddady S, Truman C, Sparling YH, Wartofsky L, Session RB, Ringel MD. Prognostic importance of vascular invasion in papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 2000; 126:309-12
21. Shaha AR, Loree TR, Shah JP. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery 1995; 118:1136-8

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