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The micropapillary/hobnail variant of papillary thyroid carcinoma: A review of series described in the literature compared to a series from one southern Italy pathology institution

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Abstract Papillary thyroid carcinoma (PTC) has a good prognosis with a 10-yr survival greater than 90%. Recently, a micropapillary pattern with hobnail appearance (MPHC) in PTC has been indicated as associated with poor prognosis, but this suggestion is based only on a few cases from geographical areas different from ours. Two-hundred ninety-nine consecutive PTC cases were collected between the years of 1992 and 2014 at our institution. The corresponding histologic sections (at least 6 for each case) were stained with hematoxylin and eosin and reviewed independently by two pathologists to reach a consensus on the identification and quantification of the MPHC. As done in other cohorts, parallel serial sections were stained with antisera for thyroglobulin, epithelial membrane antigen, thyroid-transcription-factor-1 and Ki 67. BRAF gene mutation at codon 600 and RET/PTC1 gene rearrangements were searched. A comparative statistical analysis was done between the present series and previously published series. Of the 295 PTC, 124 (42.5%) were follicular, 104 (35%) classic, 34 (11.5%) sclerosing, 15 (5%) tall cells, 10 (3.4%) Warthin-like, and 8 (2.7%) MPHC. Four MHPC cases (50%) harbored the BRAF V600E variant, while one was positive for RET/PTC1 rearrangement. Our rate of MPHC-PTC (2.7%) is 2X to 8X greater than those reported previously for cohorts from North America + North Italy, Korea and Mexico. MPHC prognosis appears to be better compared to other cohorts, probably due to not only to the lower rate of the vascular invasion, but also to the smaller size of the MPHC-PTC nodule.

Keywords Micropapillary · Hobnail · Thyroid · Papillary carcinoma · Prognosis

1 Introduction

Incidence rates of thyroid carcinomas have increased appreciably over the last few decades [1–3]. If recent trends are maintained, thyroid cancer may become the fourth most common cancer by 2030 in the United States [4]. Conversely, mortality rates have declined progressively in most areas of the world, likely due to improved diagnosis, management and treatment [5]. Among thyroid tumors, the papillary carcinoma (PTC) represents the most common histotype and the less malignant, which has a 5-year survival rate greater than 98% in Europe or North America [1–3]. However, unfavorable clinical and histologic features only occur in few patients, mainly in those affected by aggressive variants of PTC, such as diffuse the sclerosing, tall or columnar cell variant [6, 7]. Moreover in PTC, a newly described entity has been defined as micropapillary/hobnail variant (MPHC), which is characterized by the presence of small papillary clusters surrounded by lacunar spaces, hobnail features and high nuclear/cytoplasmic ratio [6, 7]. This MPHC subtype of PTC has been considered aggressive and rare, although its prevalence accounts for less than 1% of the whole PTC hystotype based on the few series reported in the literature [6–11].

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In brief, we wished to ascertain the rate and main characteristics of the MHPC variant in our cohort of PTC from patients living in the southern most region of Italy (Sicily), and compare these indices with those of the few cohorts reported in the literature.

2 Materials and methods

A total of 295 consecutive PTC cases were collected between the years of 1992 and 2015. Of these, 242 (82%) were females and 53 (18%) males (F:M ratio = 4.7:1), with a mean age of 50 years (range 14–92). The corresponding histologic sections (at least 6 for each case) were stained with hematoxylin and eosin. Of the 295 PTC, 124 (42.5%) were codified as follicular variant, 104 (35%) as classic PTC, 34 (11.5%) as sclerosing, 15 (5%) as tall cells, 10 (3.4%) as Warthin-like, and 8 (2.6%) as micropapillary/hobnail variant. Stained sections of this last variant were reviewed independently by two pathologists in order to identify and quantify the MPHC pattern (that is, at least ≥30% of the tumor, as defined by Asioli et al. [6]). Consequently, a cohort of 8 MPHC was identified and selected for the present study. These 8 cases were from 8 patients who were thyroidectomized in the years 2010 to 2015.

Additional 4 μ-thick serial sections mounted on silane-coated slides were cut and stained with the following antisera: thyroglobulin (TG; Dako, Glostrup, Denmark, clone DAK-Tg6, working dilution: w.d. 1:200), epithelial membrane antigen (EMA; Dako, clone E29, w.d. 1:50), thyroid-transcription-factor-1 (TTF-1; Dako, clone 8G7G3/1, w.d. 1:200) and Ki 67 (Dako, clone MIB-1, w.d. 1:200). The nuclear counterstain was performed by Mayer's hematoxylin. Immunoreactions were performed according to standardized procedures by an automated immunostainer (Dako autostainer Link48) and developed by EnVision detection system (Dako), utilizing 3-3′diaminobenzidine tetrahydrochloride as chromogen as elsewhere suggested [12–15].

2.1 BRAF analysis

In order to evaluate BRAF mutational status, four 10 μm thick H&E-stained sections were microdissected by scalpel using an inverted microscope in order to collect only regions with the highest MPHC representation; distant nonneoplastic thyroid tissue was utilized as control. DNA extraction was performed by QIAamp DNA FFPE Tissue kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's recommendations and DNA quantified by fluorometry with the Qubit® platform (Life Technologies, CA, USA). DNA samples were subjected to BRAF mutational analysis utilizing the BRAF Codon 600 Mutation Analysis Kit II (EntroGen, Inc, CA, USA) that allows to identify five BRAF somatic mutations in codons 600 (V600D, V600E, V600K, V600M, V600R). The amplifications were carried out in a StepOnePlus™ Real-Time PCR system (Life Technologies) following the manufacturer's procedures and the recommendations of both the Italian Association of Medical Oncology (AIOM) and the Italian Society of Pathology and Cytology (SIAPEC). Moreover, BRAF mutation negative cases were analyzed for RET/PTC gene rearrangement by the RNA extraction as elsewhere reported [16], followed by RT-PCR.

2.2 Statistical analysis

All data were analyzed by using the SPSS package version 6.1.3 (SPSS, Chicago, IL, USA). A comparative statistical analysis was done between our series and the series published previously [6–11]. A P value less than 0.05 was considered statistically significant, while a P value between 0.10 and 0.05 was considered borderline significant.

3 Results

Upon reviewing the 295 PTC, the two pathologists agreed on the identification of six variants: 124 (42.5%) were follicular, 104 (35%) classic, 34 (11.5%) sclerosing, 15 (5%) tall cells, 10 (3.4%) Warthin-like and lastly 8 (2.7%) MPHC. Relevant data of the MHPC variant regarding age, sex, gross pathology, tumor stage and post-surgery radiotherapy are reported in Table 1. Mean age was 55 years, women outnumbered men by factor of 3, and the preferred localization was the left lobe (50% of cases). The maximum diameter, a proxy of tumor size, ranged from 10 to 32 mm (mean 17.75 mm). At surgery, two cases exhibited cervical lymph node metastases (cases no. 5 and 7). Neither recurrences nor distant metastases were recorded over a follow-up period that ranged from 39 to 60 months (mean 47.75) (Table 1). Histologically, the MPHC group showed a percentage of hobnail feature (Fig. 1a, b) varying from 30 to 70% (mean 41.87) characterized by a micropapillary architecture, the papillae with vascular cores were covered by neoplastic elements with abundant eosinophilic cytoplasm and high N/C ratio; occasionally, grooved nuclei with intranuclear holes were also observed. There was an evident direct correlation between the maximum diameter of the MPHC nodule and the percent MPHC pattern ($r = 0.57$, $P = 0.14$; data not shown). No atypical mitoses neither necrosis were encountered. Upon careful histological review of the 8 MHPC cases, the two pathologists agreed on the coexistence of two types of lesions, namely hyperplastic nodules (6/8 = 75%) or chronic lymphocytic thyroiditis (CLT; 2/8 = 25%).

By immunohistochemistry, all MPHC cases expressed thyroglobulin (cytoplasm) and TTF-1 (nucleus). EMA was positive in all cases with a peculiar usual membrane staining. The proliferative index measured by Ki67 antibody ranged from 2 to 20% (mean 6%) of the neoplastic elements (Fig. 2).

The rate of the BRAF p.V600E (c.1799T>A) mutation was 4/8 MHPC cases (50%) (Table 1). These 4 BRAF-mutated

Table 1 Clinicopathological, mutational and outcome characteristics of our MPHC series

No	Sex	Age	Site	Size (mm)	LI	% MPHC pattern	BRAF status	pTNM	Nodal MTS	Recurrence	Distant MTS	Postsurgical RT	Coexisting disease	FU (Mo)
1	F	61	Isthmus	12	NO	30	WT	T1bN0	NO	NO	NO	NO	HG	AND (44)
2	M	47	Left lobe	15	NO	30	WT	T1bN0	NO	NO	NO	NO	HG	AND (41)
3	F	69	Left lobe	10	YES	40	MUT	T1aN0	NO	NO	NO	NO	HG	AND (39)
4	F	46	Bilateral	25	NO	35	WT*	T2N0	NO	NO	NO	NO	HG	AND (42)
5	F	55	Right lobe	14	YES	60	MUT	T1bN1a	YES	NO	NO	YES	CLT	AND (52)
6	M	60	Left lobe	22	NO	40	WT	T2N0	NO	NO	NO	NO	HG	AND (60)
7	F	52	Left lobe	32	YES	70	MUT	T2N1a	YES	NO	NO	YES	CLT	AND (48)
8	F	50	Right lobe	12	YES	30	MUT	T1bN0	NO	NO	NO	NO	HG	AND (56)

Abbreviations: F female; *M* male; *LI* lymphatic invasion; *WT* wild type; *WT** wild type with RET/PTC1 gene rearrangement; *MUT* mutated; *HG* hyperplastic goiter; *CLT* chronic lymphocytic thyroiditis; *RT* radiotherapy; *MTS* metastases; *FU* follow-up; *Mo* months; *AND* alive with no disease

cases showed lymphatic invasion, with 2/4 presenting lymph node metastases at surgery. Among the 4 BRAF negative cases, only one exhibited RET/PTC1 gene rearrangement.

Table 2 summarizes the comparison of our 8 cases with the other 66 MPHC cases from six studies appeared in the English-language literature [6–11]. With two exceptions [7, 11], the F:M ratio is 3:1 and mean age comprised between 54 and 58 years. Our series stands out for the smallest diameter of the tumor (tied with the Korean series), lowest proportion of patients at stage IV (0%), and lowest proportion of patients with recurrent disease (0%). Though the follow-up of the Korean series was shorter compared to ours (9 to 28 months [median 12 months], vs. 39 to 60 months [mean 47.7], the Korean patients resemble our patients for the low rate of recurrence (10%), absence of distant metastases and high rate of disease-free survival (90%).

4 Discussion

A peculiar micropapillary neoplastic architectural pattern (MPC), firstly described in the mammary gland by Siriaunkgul & Tavassoli [17], was recognized as a distinct entity also in other organs, including the bladder, lung, pancreas, parotid gland, gallbladder, colorectum, ovary and stomach [17–21]. In most of these organs, studies have documented a frequent association of MPC with lymphovascular invasion, high propensity for lymph-node metastasis and consequent reduction in survival and increased mortality with poor clinical outcome [18–22].

In the thyroid literature, small-sized series of MPHC were reported, and they were characterized by a typical micropapillary growth pattern, hobnail appearance, inversion of cellular polarity, enlarged eosinophilic cytoplasm and nucleus/cytoplasm ratio [6–11].

Although MPHC has been only recently identified as a very rare PTC variant, its clinico-pathologic features suggested an aggressive behavior, as documented by larger volume, extrathyroidal extension, increased rate of spread to lymph nodes and distant organs [6–11]. Our rate of the MPHC variant is 2.7% of the whole PTC cohort. This frequency is 2X to 8X greater than those reported in previous series from South Korea (0.34%, $P = 2.2 \times 10^{-7}$) [11], North America/North Italy (0.7%, $P = 0.0002$) [8], North America (≈1%; exact denominator not given) [10] or Mexico (1.4%, $P = 0.19$) [7].

Another interesting finding of our MPHC series is represented by the smaller size of the neoplastic nodules compared to that of the other series, with the exception of the South Korea series [11]. Probably, the smaller size of MPHC at the time of thyroidectomy contributes to the best outcome of the disease in our MPHC cohort. This is similar to the data form of the Korean series [11], in which a mean maximum diameter of 16.3 mm was associated with a disease-free survival equal to

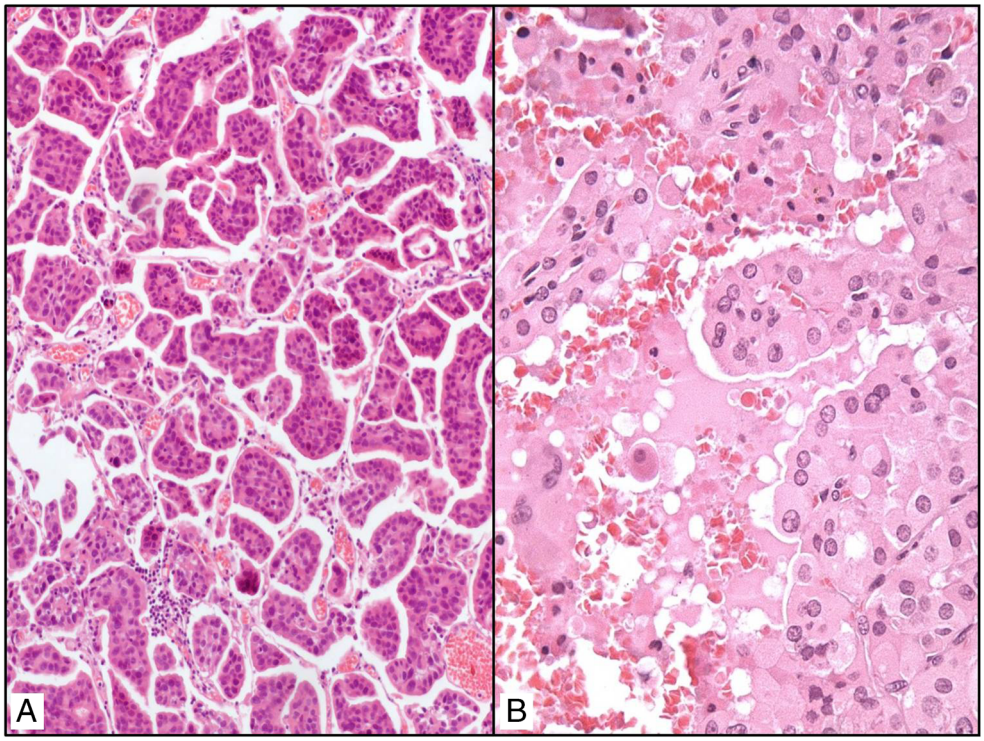

Fig. 1 PTC characterized by a predominant micropapillary pattern (**a** H&E, X200) and prominent hobnail features with growed nuclei and eosinophilic cytoplasm (**b** H&E, X200)

90%. Moreover, in our MPHC cohort, the mean Ki67 value was 6%, lower than values reported in other MPHC cohorts. [6, 7]. Consequently, taking into account the well-known direct correlation between expression of Ki67 and both metastatization and unfavorable prognosis in papillary thyroid microcarcinoma [11], the lower Ki67 percentage represents an additional explanation for the absent aggressive behavior in our MPHC cohort.

In all 4 MHPC patients having the intratumoral BRAFV600E mutation, the tumor was complicated by lymphatic invasion, and in 2/4 by the cervical lymph nodes spread. These two cases with lymph node involvement featured the highest proportion of MHPC pattern (60-70%), greater than the 30-40% range of the remaining 6 cases with no spread to lymph nodes. Of note, the two BRAF V600E-positive MHPC that had no cervical lymph node metastasis despite an evident lymphatic invasion, had a maximum diameter of 10 and 12 mm, while the two BRAF V600E-positive MHPC that spread to cervical lymph nodes had a maximum diameter of 14 and 32 mm. Of interest, within the 48–52 months of follow-up, these two patients had no disease recurrence. This favourable outcome could have been favored by the concurrent chronic lymphoctic thyroidits (CLT), the only two patients in whom this coexistence occurred. Indeed, CLT is known as an independent predictor for less aggressiveness in conventional PTC patients regardless of BRAF mutation status [23–27].

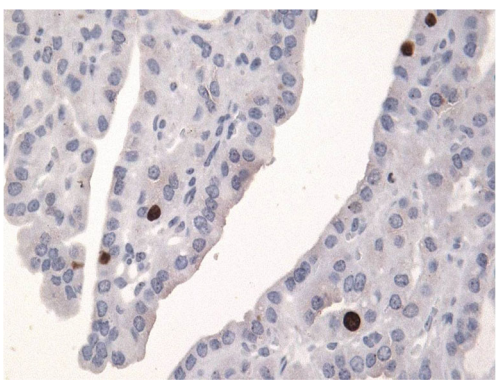

Fig. 2 Ki-67 nuclear immunoreactivity was rarely revealed (immunoperoxidase, Mayer's haemalum counterstain, X400)

In PTC patients from several geographical areas, BRAFV600E mutation was significantly correlated with known clinicopathological poor prognostic factors, such as extrathyroidal extension, lymph node metastasis and advanced stage [23–32]. By contrast, this unfavorable correlation was not confirmed in other studies [33, 34]. Therefore, it is not surprising that interstudy differences may also apply to the prognostic significance of the BRAFV600E in the setting of the MPHC subtype. In any case, this BRAF mutation represents an early step during thyroid micropapillary carcinogenesis because it is detectable also in small size neoplasms, including those such as our cases, characterized by lymphatic or lymph node colonization. Moreover, the prognostic implications of BRAF mutation have been underlined in T1 papillary carcinomas, which are tumors of 2 cm or less in size; in this category, incidentally discovered papillary microcarcinomas measuring 1 cm or less have been encompassed [35–40]. Finally, among our BRAF negative cases, only one exhibited RET/PTC1 gene rearrangement.

Table 2 Comparative analysis among our series and others previously published

	F:M ratio	Mean age, years (range)	Mean tumor size, mm (range)	Tumor site	Mean % MPHC pattern (range)	LI	Nodal MTS	AJCC Stage	Reccurence	Distant MTS	BRAF mutation	Mean follow-up, months (range)	Outcome
Present study Italy	3:1	55 (46–69)	17.75 (10–32)	Left lobe (4/8) 50% Right Lobe (2/8) 25% Isthmus (1/8) 12.5% Bilateral (1/8) 12.5%	41.87 (30–70)	(4/8) 50%	(2/8) 25%	I (4/8) 50% II (2/8) 25% III (2/8) 25% IV 0	0	0	(4/8) 50%	47.75 (39–60)	AND (8/8) 100%
Asioli et al. 2010 Italy/USA	3:1	57.6 (28–78)	25 (10–40)	NS	67.5 (30–100)	(7/8) 87.5%	(6/8) 75%	I (0/8) II (1/8) 12.5% III (2/8) 25% IV (5/8) 62.5% c	(3/8) 37.5%	(5/8) 62.5% f	(4/8) 50%	77.2 (4–236)	DOD (4/8) 50% AND (2/8) 25% i AWD (2/8) 25%
Lino-Silva et al. 2012 Mexico	1:1.3	45 (27–68)	43.5 (39.5-50.5)	NS	12.1 (5–20)	(5/7) 71.5%	(5/7) 71.5%	I-II 2/7 (28%) III-IV 5/7 (72%) d	NS	(3/7) 42.8% g	NS	103 (40–158)	DOD (4/7) 57.2% AWD (3/7) 42.8%
Asioli et al. 2013 Italy/USA	3:1	57.3 (28–78)	22.95 (10–70)	Bilateral (14/24) 58.3%	(10–100)	(17/24) 70.8%	(7/24) 29.1%	I-II 9/24 (37.5%) III-IV 15/24 (62.5%) e	NS	(8/24) 33.3% h	NS	106 (4–274)	DOD (8/24) 33.3% AND (9/24) 37.5% j AWD (6/24) 25% DND (1/24) 4.2%
Lubitz et al. 2014 USA	3:1	54.1 (21–80)	37 (5–65)	NS	61.5 (40–100)	(5/12) 42%	(10/12) 83.3% a	I (5/12) 42% II (0/12) III (3/12) 25% IV (4/12) 33%	(4/12) 33%	(3/12) 25%	(8/11) 73%	26.5 (14–35.5)	DOD (1/11) 9,2% AND (7/11) 63.6% k AWD (3/11) 27.2%
Asioli et al. 2014 Italy	1.5:1	65 (27–86)	42 (20–90)	NS	27 (10–50)	(4/5) 80%	(3/5) 60%	NS	(1/5) 20%	0	(3/5) 60%	8 (2–24)	AND (4/5) 80% AWD (1/5) 20%
Lee et al. 2015 South Korea	1.5:1	50.4 (32–68)	16.3 (6–40)	Right lobe (6/10) 60% Left lobe (4/10) 40%	NS	(8/10) 80%	(8/10) 80% b	I (4/10) 40% II (0/12) III (4/10) 40% IV (2/10) 20%	(1/10) 10%	0	(8/10) 80%	12 (9–28)	DOD (0/10) AND (9/10) 90% AWD (1/10) 10%

Abbreviations: F female; *M* male; *LI* lymphatic invasion; *MTS* metastases; *NS* not specified; *AND* alive with no disease; *DOD* dead of disease; *AWD* alive with disease; *DND* dead not of disease

[a b] By Fisher's exact test (df = 2), P 0 0.19 or $P = 0.05$ vs our 25%

[c] By $\chi 2$ test (df = 3),, $\chi 2 = 9.33$, $P = 0.25$ vs our 4-stage distribution

[d e] By Fisher's exact test (df = 2), $P = 0.0047$ or $P = 0.017$ vs. our 2-stage distribution

[f g h] By Fisher's extact test (df = 2), $P = 0.026$, $P = 0.07$, or $P = 0.08$ vs. our 0%

[i j k] By Fisher's exact test (df = 2), $P = 0.007$, $P = 0.003$, $P = 0.10$ vs our 100% rate of alive with no disease (AND)

In our MPHC series, we have noticed the coexistence of two thyroid lesions, hyperplastic nodules (75%) or chronic lymphocytic thyroiditis (25%). Since the coexistence of other lesions was disregarded by the other studies [6–11], we cannot contrast our data with the literature. Nevertheless, in recent studies, the presence of CLT in patients with PTC was reported to be associated with lower recurrence rate of PTC and improved survival rate [41–47]. Indeed, in the presence of CLT, PTC is associated with pathologic markers of decreased tumor aggressiveness, such as small tumor size and low stage, no extrathyroid extension, no lymph node metastases, better locoregional control, lower rates of recurrence and greater overall and disease-free survival [41–47]. A similar clinical behavior was found in our MPHC series, in which no recurrences, distant metastasis or cancer-related mortality were observed, even if two cases had metastatic lymph nodes.

In conclusion, our Sicilian MPHC series is the only one with the highest representativity (almost 3%) within the whole PTC hystotype. Because our cohort was collected in a recent period that spanned the years 2010 though 2015, we cannot have a long follow-up duration. However, within an average of 4 years after thyroidectomy, 100% of the patients were still alive with no disease. Unlike the generality of the literature, our MHPC cases feature a good prognosis.

Compliance with ethical standards

Conflict of interest None.

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