



Papillary Thyroid Microcarcinoma: Clinico-pathological Correlation with *BRAF* V600E Mutation



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ABSTRACT

Background: Papillary thyroid microcarcinoma (PTMC: papillary carcinoma \leq 1cm) are increasingly being detected due to the frequent use of ultrasonography. Their biology and management remains controversial despite the excellent prognosis. In recent years *BRAF* V600E mutation has emerged as a marker of aggressive behavior in papillary thyroid carcinoma (PTC) but its significance in PTMC is not clear.

Design: Clinical and histopathological features were reviewed in 129 PTMCs. The latter included histologic variant, tumor interface with non-neoplastic thyroid, nuclear features of PTC (well-developed or subtle), presence of cystic change, tall or polygonal eosinophilic (plump pink) cells, extrathyroidal extension (ETE), tumor-associated fibrosis/sclerosis/desmoplasia, stromal calcification, psammoma bodies and osteoclast-like multinucleated giant cells. These features were correlated with *BRAF* V600E mutational analysis performed in all cases by single strand conformational polymorphism.

Results: Table[†] summarizes significant clinico-pathological differences in *BRAF* V600E mutation positive and negative PTMCs. No significant difference was found between the two groups of PTMCs in age, sex, tumor size, multifocality, psammoma bodies, stromal calcification, multinucleated giant cells and polygonal eosinophilic tumor cells.

BACKGROUND

In the last few decades, there has been a steady rise in the incidence PTMC, mainly attributed to increased diagnostic scrutiny including widespread use of thyroid ultrasonography coupled with fine needle aspiration. PTMC has excellent prognosis with survival rates almost similar to the general population. Only a subset of PTMCs shows locoregional recurrence/persistence with significant morbidity. This poses a challenge for the identification of the aggressive subset and their optimal management. *BRAF* V600E mutation has emerged as a marker of aggressive behavior in PTC. However, its exact significance in PTMC is not entirely clear. The purpose of this study is to review the prevalence of *BRAF* V600E mutation in PTMC, perform a histopathological correlation with mutation and to explore its possible association with aggressive features.

METHODS

129 consecutive PTMC cases that were *BRAF* V600E mutation tested during January 2010 – November 2011 were reviewed by two pathologists blinded to the *BRAF* V600E mutation results. The clinical and histopathologic features are listed in Tables 1 - 4. *BRAF* analysis was done by single strand conformational polymorphism.

RESULTS

Tables 1 through 4 summarize differences in *BRAF* V600E mutation positive and negative PTMCs.

Table 1. Patient Demographics and Tumor Characteristics in 129 PTMC

	<i>BRAF</i> V600E mutation positive (n=90; 69.7%)	<i>BRAF</i> V600E mutation negative (n=39; 30.3%)	p value
Age (years)			
Mean (range)	50 (23-80)	48 (13-81)	0.34
≤ 45 years (n=48)	35/90 (39%)	13/39 (33%)	0.33
>45 years (n=81)	55/90 (61%)	26/39 (67%)	0.69
>45 year with >5 mm tumor (n=60)	46/90 (51%)	14/39 (36%)	0.18
Female: Male (103:21)	71:16 (4.4:1)	32:5 (6.4:1)	0.45
Location:			
Right lobe (n=58)	39/90 (43%)	19/39 (49%)	0.70
Left lobe (n=54)	38/90 (42%)	17/39 (43%)	0.84
Isthmus (n=16)	13/90 (15%)	3/39 (8%)	0.39
Tumor size (mm):			
Mean (range)	6.6 (1 – 10)	6.1 (1 – 10)	0.22
≤ 5mm (n=37)	22/90 (24%)	15/39 (38%)	0.14
>5mm (n=92)	68/90 (76%)	24/39 (62%)	0.14
Multifocality (n=61)	45/90 (50%)	16/39 (41%)	0.44
Mean number of foci (range)	2.8 (2- >5)	2.1 (2-3)	-

Table 2. Lymph Node Status in 89 PTMC (pN)

Lymph Node Status (n=89/129, 69%)	<i>BRAF</i> V600E mutation positive (n=62/90, 69%)	<i>BRAF</i> V600E mutation negative (n=27/39, 69%)	p value
Positive Lymph Nodes (n=26/89; 29%)	23/62 (37%)	3/27 (11%)	0.02
Central Lymph Nodes: pN1a (n=15)	12/62 (19%)	3/27 (11%)	0.53
Lateral Lymph Nodes: pN1b (n=11)	11/62 (18%)	0/27 (0%)	0.03

Percentages rounded off to the nearest full numbers

Table 3. Histopathological Features of 129 PTMC			
Histopathological features	<i>BRAF</i> V600E mutation positive (n=90)	<i>BRAF</i> V600E mutation negative (n=39)	p value
Tumor interface with non-neoplastic thyroid			
Well circumscribed tumors including encapsulated tumors (n=28)	12/90 (13%)	16/39 (41%)	0.001
Completely encapsulated tumors (n=18)	11/90 (12%)	7/39 (18%)	0.41
Infiltrative tumor borders (n=101)	78/90 (86%)	23/39 (59%)	0.001
Architecture			
Cystic change (n=54)	43/90 (48%)	11/39 (28%)	0.05
Back to back arrangement (n=34)	26/90 (29%)	8/39 (21%)	0.39
Tumor Stroma			
Desmoplasia with or without sclerosis and/or fibrosis (n=43)	35/90 (39%)	8/39 (21%)	0.04
Fibrosis/sclerosis/desmoplasia (n=105)	80/90 (89%)	25/39 (64%)	0.002
Stromal calcification (n=43)	32/90 (35.5%)	11/39 (28%)	0.5
Psammoma bodies (n=55)	39/90 (43%)	16/39 (41%)	0.85
Tumor associated lymphocytes (n=54)	33/90 (37%)	21/39 (54%)	0.08
Tumor Cell Morphology			
Classic nuclear features (n=125)	90/90 (100%)	35/39 (90%)	0.008
Plump eosinophilic cells (n=63)	49/90 (54%)	14/39 (36%)	0.058
Tall cell features (n=12)	11/90 (12%)	1/39 (2.5%)	0.1
Other Features			
Extrathyroidal extension (n=18)	17/90 (19%)	1*/39 (2.5%)	0.01
Intratumoral multinucleated giant cells (n=52)	41/90 (45.5%)	11/39 (28%)	0.08
Lymphovascular invasion (n=17)	14/90 (15.5%)	3/39 (8%)	0.27
Additional thyroid pathology (n=102)	68/90 (76%)	34/39 (87%)	0.16

*This tumor was tested twice for *BRAF* V600E mutation.

Table 4. Correlation of *BRAF* V600E Mutation with Histologic Subtypes

PTMC subtypes (n=129)	<i>BRAF</i> positive (n=90; 70%)	<i>BRAF</i> negative (n=39; 30%)
Classic (n=61; 47%)	46 (75%)	15 (25%)
Follicular (n=14; 11%)	3 (21%)	11 (79%)
*Subcapsular sclerosing (n=17; 13%)	12 (71%)	5 (29%)
§Occult sclerosing (n=13; 10%)	10 (77%)	3 (23%)
Tall cell (n=11; 8.5%)	10 (91%)	1 (9%)
Others (n=13, 10%)	9 (69%)	4 (31%)

†Subcapsular sclerosing variant (SSV) was defined as non-cystic PTMC with a peripheral subcapsular location, abutting and involving the thyroid capsule along at least 20% of the tumor's circumference, a sclerosing pattern of infiltration, usually with a central stellate scar, and with no or few papillae.

§Occult sclerosing variant was differentiated from SSV by its more central intraparenchymal location.

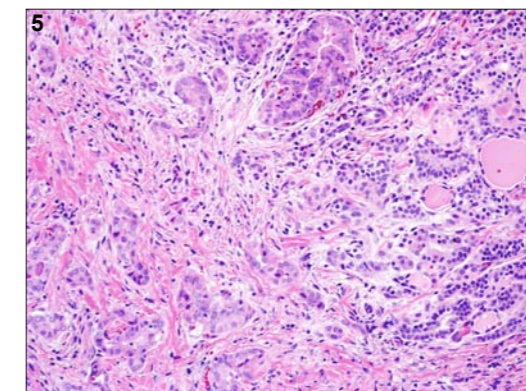
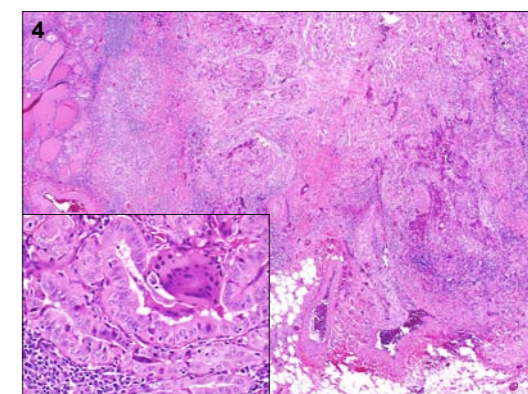
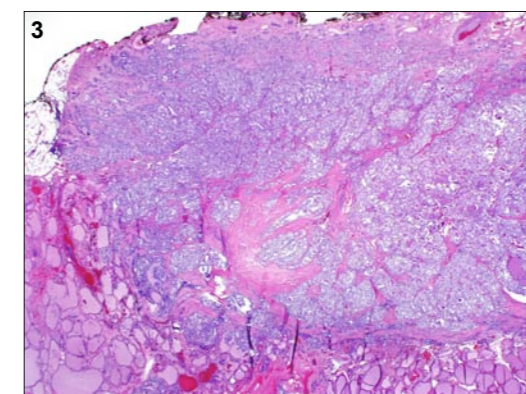
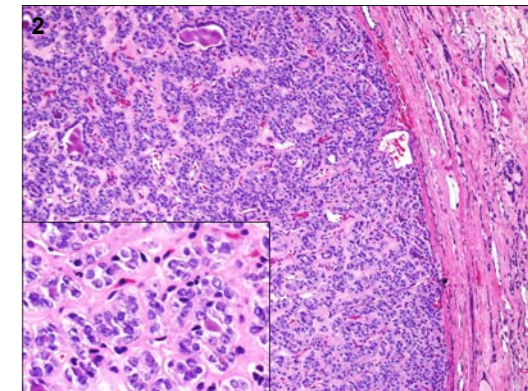
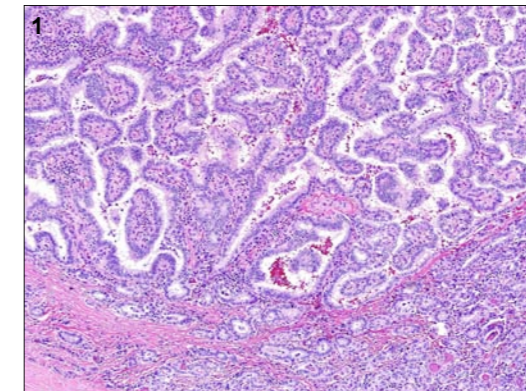


Figure 1: Classic variant with well-developed papillary cores lined by tumor cells with characteristic nuclei.

Figure 2: Follicular variant with exclusively follicular architecture and fibrous capsule at the periphery. Inset shows subtle nuclear features of PTC.

Figure 3: Subcapsular sclerosing variant with extrathyroidal extension and stromal fibrosis.

Figure 4: Tall cell variant with abundant stromal fibrosis/sclerosis. Tumor cells with height at least twice the width and with abundant pink cytoplasm (inset). Multinucleated giant cell (arrow) is present.

Figure 5: Plump pink cells at the infiltrating edge of the tumor associated with desmoplasia: The tumor cells consist of moderate amount of pink cytoplasm, but do not fulfill the criteria for tall cells.

CONCLUSIONS

- The prevalence of *BRAF* V600E mutation in papillary thyroid microcarcinoma is similar to larger (>1 cm) papillary thyroid carcinoma at our institution.
- The morphology of mutated microcarcinomas is distinctive and characteristic histological features include infiltrative interface with non-neoplastic thyroid, stromal fibrosis/sclerosis/desmoplasia, and well-developed characteristic nuclear features of PTC.
- BRAF* V600E mutation was significantly more prevalent in subcapsular sclerosing, tall cell and classic variant when compared with follicular variant of PTMC.
- Similar to PTC, presence of *BRAF* V600E mutation in PTMC is associated with aggressive features such as extrathyroidal extension and nodal metastasis, including lateral cervical lymph node metastasis

†Updated values, *Lymph nodes were available in 89 PTMCs

Conclusion: *BRAF* V600E mutation was significantly associated with the subcapsular sclerosing variant of PTMC but not with the follicular variant, and with lymph node metastasis. Histological features characteristic of *BRAF* V600E mutation positive tumors included infiltrative interface with non-neoplastic thyroid, stromal fibrosis/sclerosis/desmoplasia and well-developed characteristic nuclear features of PTC.