# Can Tall Cell Microcarcinoma be Diagnosed on Fine Needle Aspiration? An Analysis of Clinicopathological Features, Preoperative Fine Needle Aspiration and Genetic Alteration

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## ABSTRACT

**Background:** Thyroid papillary microcarcinomas are by definition equal to or less than 1.0 cm in size. These are often considered incidental and clinically insignificant. Tall cell variant of papillary thyroid carcinoma is a rare variant that is associated with a more aggressive behavior and often presents at an advanced stage. Recently we described the tall cell variant of papillary thyroid microcarcinoma (microTCV). Despite their small size, microTCV displayed aggressive pathological features. This study was designed to determine if microTCV have features sufficiently characteristic for their preoperative diagnosis as this would help to plan an appropriate surgical strategy.
**Design:** microTCV cases over the last 10 years were identified from our files. The cytology slides were reviewed and the findings were correlated with clinicopathologic features and with results of BRAF V600E mutation analysis.
**Results:** Twenty-one cases were identified (18 females and 3 males). The average age of patients was 53 years (range, 34-73 years). All patients underwent total thyroidectomy. Thirteen of the thyroids contained multifocal microTCV. Tumor size ranged from 0.2 cm to 0.9 cm (mean, 0.70 cm). Background lymphocytic thyroiditis was present in 10 cases. At presentation 29% had lymph node metastasis, vascular invasion was present in 19% while extrathyroidal extension was present in 38% of cases. Fifty eight percent of cases had smears with papillary groups while 68% showed cohesive flat sheets. The frequency of cytologic features were as follows: nuclear grooves – 90%; abundant dense eosinophilic cytoplasm – 90%; nuclear enlargement – 74%; nuclear pseudoinclusions – 74%; irregular nuclear membranes – 47%; powdery chromatin – 42%; crowding and overlapping – 42%. Twenty cases (95%) were positive for BRAF V600E mutation.
**Conclusions:** microTCV is frequently associated with multifocality, extrathyroidal extension, and lymph node involvement at presentation and high BRAF mutation rate, hence the need for recognition on FNA. Features with high diagnostic yield include cohesive flat sheets, abundant dense eosinophilic cytoplasm, nuclear enlargement and grooves, among others.

## BACKGROUND

Thyroid papillary microcarcinomas are by definition equal to or less than 1.0 cm in size. These tumors are often considered incidental and clinically insignificant. However, the tall cell variant of papillary thyroid carcinoma is a rare variant associated with a more aggressive behavior. These patients often present at an advanced stage. Recently we described the tall cell variant of papillary microcarcinoma (microTCV). Despite their small size, microTCV display the aggressive pathological features associated with tall cell variant tumors of a larger size.

Several papers have described the cytologic features characteristic of tall cell variant (TCV) of papillary thyroid carcinoma (PTC) compared with those of classic variant of papillary thyroid carcinoma. These have reported that a high number of elongated cells, oncocytic cytoplasm, nuclear grooves and pseudoinclusions have been useful in identifying the TCV of PTC by fine needle aspirate. However, none have addressed whether or not those features are identifiable in microcarcinomas. It would be clinically valuable to be able to identify these tumors by fine needle aspiration so that patients might benefit from adequate staging work-ups and surgical planning. This current study was designed to determine if microTCV have features sufficiently characteristic for their preoperative diagnosis as this would help to plan an appropriate clinical strategy.

## DESIGN

MicroTCV cases over the last 10 years were identified from our files. The cytology slides were reviewed and the findings were correlated with clinicopathologic features and with results of BRAF V600E mutation analysis.

Twenty-one cases of histologically proven microTCV with prior fine needle aspiration cytology were identified. Cytology reports were reviewed to extract demographic parameters and pathologic characteristics of the tumor. Histologic slides were reviewed to confirm the diagnosis of microTCV. The fine needle aspiration cytology materials of these cases were then reviewed, when available. Ten groups of cells were examined per case with each group having at least 50 cells. Eight cytologic features were scored: nuclear enlargement (NE), nuclear contour irregularity (NCI), nuclear crowding/overlapping (NCO), nuclear pseudoinclusions (NPI), chromatin clearing (CC), nuclear grooves (NG), nucleoli (NUC) and presence of abundant cytoplasm (CYTO). They were scored as 0,1, 2 and 3 when present in none, <10%, 10-50%, and >50% of tumor cells, respectively.

## RESULTS

Twenty-one cases were identified. Patients had a median age of 53 years. Clinicopathologic and molecular features are summarized in **Table 1**. All patients underwent total thyroidectomy. Thirteen of the thyroids contained multifocal microTCV. Tumor size ranged from 0.2 cm to 0.9 cm (median, 0.7 cm). Fifty-eight percent of cases had smears with papillary groups while 68% showed cohesive flat sheets. The frequency of cytologic features and grading of those features are described in **Tables 2** and **3**.

**Table 1. Clinico-pathologic and Molecular Characteristics of microTCV**

| | |
|---|---|
| Median age (years) | 53 (range: 34-73) |
| Female: Male | 18:3 |
| Median tumor size in mm (range) | 7 (2-9) |
| Background Lymphocytic Thyroiditis | 10/21 (47.6%) |
| Lymph Node Metastases | 6/21 (28.6%) |
| Lymphovascular Invasion | 4/21 (19.0%) |
| Extrathyroidal Extension | 8/21 (38.1%) |
| *BRAF* V600E mutation positive | 20/21 (95.2%) |
| AJCC Stage | |
| I | 16/21 (76.2%) |
| III | 4/21 (19.0%) |
| IVA | 1/21 (4.8%) |

**Table 2. Cytologic Features of microTCV**

| | |
|---|---|
| Nuclear Grooves | 19/21 (90.5%) |
| Abundant Cytoplasm | 19/21 (90.5%) |
| Nuclear Enlargement | 19/21 (90.5%) |
| Nuclear Pseudoinclusions | 16/21 (76.2%) |
| Irregular Nuclear Membranes | 10/21 (47.6%) |
| Cleared Chromatin | 9/21 (42.9%) |
| Nuclear Crowding & Overlapping | 9/21 (42.9%) |

**Table 3. Prevalence of Cytologic Features in Fine Needle Aspirates from microTCV**

| Feature | Average Score |
|---|---|
| Nuclear Enlargement | 3.0 |
| Nuclear Contour Irregularity | 2.2 |
| Nuclear Crowding/Overlapping | 2.6 |
| Nuclear Pseudoinclusions | 0.2 |
| Chromatin Clearing | 3.0 |
| Nuclear Grooves | 2.7 |
| Nucleoli | 3.0 |
| Abundant Cytoplasm | 2.8 |

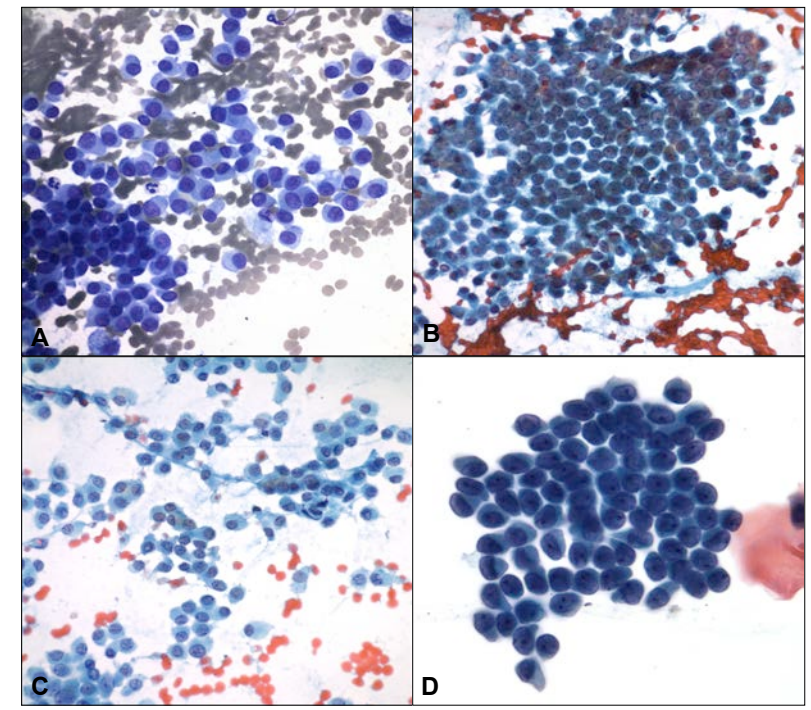


**Figure 1.** FNA biopsy of microTCV. (**A**) Sheets of cells with abundant eosinophilic cytoplasm, Papanicolaou stain, X400. (**B**) Nuclear grooves with nuclear crowding/overlapping, Papanicolaou stain, X400. (C) Nuclear pseudoinclusions, Papanicolaou stain, X400. (**D**) Elongated/enlarged nuclei with cleared chromatin, Papanicolaou stain, X1000).

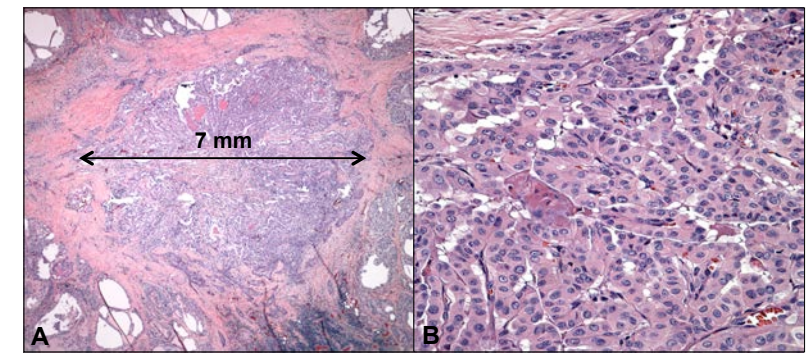


**Figure 2. (A)** Low power photomicrograph of a resected tall cell variant microTCV (H&E, x100). (**B**) Higher power magnification of the lesion with abundant dense, eosinophilic cytoplasm and nuclear grooves (H&E, x400).

## CONCLUSIONS

microTCV is frequently associated with multifocality, extrathyroidal extension, and lymph node involvement at presentation and high BRAF mutation rate, hence the need for recognition on FNA. Features with high diagnostic yield include cohesive flat sheets, abundant dense eosinophilic cytoplasm, nuclear enlargement and grooves, among others. The data presented herein displays multiple noteworthy findings, but continued study is necessary in order to better define the potential differences in cytologic findings between microTCV and larger tumors.

## REFERENCES

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