BRAF MUTATION IS POSITIVE IN A LOW PERCENTAGE OF CASES OF THE FOLLICULAR VARIANT OF PAPILLARY THYROID CANCER

Proietti A, Giannini R, Ugolini C, Miccoli M, Fontanini G, Di Coscio G, Romani R, Berti P, Miccoli P, Basolo F. **BRAF** status of follicular variant of papillary thyroid carcinoma and its relationship to its clinical and cytological features. Thyroid 2010;20:1263-70. Epub October 17, 2010.

SUMMARY • • • •

BACKGROUND AND METHODS

The follicular variant of papillary thyroid carcinoma (FVPTC) typically has a follicular pattern, and less than 1% of the tumor shows papillary formations. Yet these follicular cells have nuclear features of papillary thyroid carcinoma. The mutational status of the BRAF gene was evaluated in 187 FVPTCs diagnosed on histologic examination independently by three pathologists in Italy. Each patient had surgery after a fine-needle aspiration biopsy (FNAB) had been performed that had been classified by the British Thyroid Association Guidelines as inadequate (n = 19; Thy1), benign (n = 19; Thy2), follicular lesion/follicular lesion with atypia (n = 109; Thy3), suspicious for PTC (n = 20; Thy4), or malignant (n = 11; Thy5).

RESULTS

The BRAF mutational status (V600E, K600E, wt) correlated with the cytologic classification in 54.5% of malignant lesions, 27.6% of lesions suspicious for PTC, 12% of follicular lesions, and 9.3% of follicular

lesions with atypia. The FNABs of the first 68 cases were examined for four cytologic features: nuclear grooves, intranuclear cytoplasmic inclusion bodies, number of cells per high-power field, and mean nuclear diameter. These cytologic findings were not associated with the BRAF mutation. BRAF mutations occurred in 16.6% of FVPTC, and most of these had suspicious or positive cytology on FNAB;. 30 cases showed a V600E mutation and 1 case had a K601E mutation. The BRAF mutations were not associated with any clinicopathological parameters, including age, sex, size of tumor, extrathyroidal extension, or lymph-node metastases. Although there was extrathyroidal extension in 24.5% of the BRAF tumors compared to 15.7% of the wild type BRAF tumors, this was not statistically significant.

CONCLUSIONS

Because BRAF is mutated in a low percentage of FVPTC and most of these mutated cases are suspicious or positive on fine-needle aspiration, analysis for BRAF is of limited value in the preoperative diagnosis of FVPTC.

COMMENTARY • • • •

FVPTC is a common variant of papillary thyroid carcinoma. The presence of this variant was hotly debated for many years. Dr. Austin Vickery, a leading thyroid cytopathology expert at the Massachusetts General Hospital, refused to acknowledge this subtype. Even today, the diagnosis can be difficult despite attempts to standardize morphologic characteristics of FVPTC or use molecular characterization. This difficulty was demonstrated when 10 expert thyroid pathologists evaluated 87 cases of FVPTC: only 39 % had a concordant diagnosis (1). The BRAF point mutation occurs in classic PTC with a frequency that varies from 29% to 83%. Furthermore, BRAF has

been associated more with PTCs that have a papillary rather than the follicular pattern (2). Thus, it is not surprising that this study found BRAF mutations in only a small fraction of the FVPTC tumors. This study demonstrates that finding a BRAF mutation is seldom helpful in distinguishing benign from malignant lesions for FNABs read as "indeterminate" that result in a patient being sent to surgery for possible cancer. In fact, BRAF positivity in the FVPTC whose cytology was read as a "follicular lesion" or a "follicular lesion with atypia" was low, approximately 10%. The applicability of this data in the United States is not clear, as the cytologic interpretation in Italy may be different from what is standard in the United States. Of concern is that in this group of FVPTC, 10% had an

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FNAB that indicated benign cytology. It is not indicated why these patients had a thyroidectomy. Further, 63% of the biopsies were reported as indeterminate or insufficient, a much higher percentage than that reported in the United States (3). Another limitation of this study is the lack of clinical correlation of tumors that showed metastatic spread of the FVPTC with the presence of the BRAF point mutation. BRAF

testing of thyroid FNAB specimens may have a role in the preoperative risk stratification of PTCs, as several other studies have shown that the presence of BRAF mutation is strongly associated with extrathyroidal extension and lymph-node metastases with a poorer clinical prognosis (4,5).

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