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Review

Surgical implications of B-Raf^{V600E} mutation in fine-needle aspiration of thyroid nodules

Michal Mekel, M.D., Carmelo Nucera, M.D., Ph.D., Richard A. Hodin, M.D., Sareh Parangi, M.D.*

Thyroid Cancer Research Laboratory, Endocrine Surgery Unit, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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Abstract

BACKGROUND: Management of patients with thyroid nodules is based on establishing an accurate diagnosis; however, differentiating benign from malignant lesions preoperatively is not always possible using current cytological techniques. Novel molecular testing on cytological material could lead to clearer treatment algorithms. B-Raf^{V600E} mutation is the most common genetic alteration in thyroid cancer, specifically found in papillary thyroid cancer (PTC), and usually reported to be associated with aggressive disease.

DATA SOURCE: A literature search using PubMed identified all the pertinent literature on the identification and utilization of the B-Raf^{V600E} mutation in thyroid cancer.

CONCLUSIONS: The utility of using B-Raf mutation testing for nodules with indeterminate cytology is limited since many of those nodules (benign and malignant) do not harbor B-Raf mutations. However, when the pathologist sees cytological features suspicious for PTC, B-Raf^{V600E} mutation analysis may enhance the assessment of preoperative risks for PTC, directing a more aggressive initial surgical management when appropriate.

Thyroid nodules are common and are being increasingly detected. While most thyroid nodules are benign, surgical treatment remains common. Differentiating benign from malignant lesions preoperatively is not always possible using current imaging and cytological techniques. Novel molecular testing on cytological material could lead to clearer treatment algorithms for those with thyroid nodules and increase the efficacy of novel targeted therapies in those with malignancy. Surgeons, endocrinologists, cytologists, and medical oncologists should be familiar with recent studies on the incidence and role of B-Raf^{V600E} mutation in thyroid neoplasms, including implications for mutational analysis in fine-needle aspirations and potential alterations in therapy that may result based on this finding. Information on this mutation and its clinical role is limited, as many studies are small, retrospective, and lack controls.

Fine-needle aspiration biopsy (FNAB) is currently considered the most important and rational component of our diagnostic armamentarium for decision making in any given thyroid nodule. Its main purpose is to provide more information on the risk of malignancy in any given nodule, thus helping guide the clinician to surgical therapy (lobectomy vs total thyroidectomy, ± central compartment lymph node dissection) if necessary. The FNAB diagnostic scheme consists of 4 major categories, including benign, indeterminate, malignant, and unsatisfactory, while indeterminate cytology includes 3 subcategories, including lesion of undetermined

* Corresponding author. Tel.: +1 617 643 4806; fax: +1 617 643 4802.
E-mail address: sparangi@partners.org

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significance, follicular neoplasm, and lesion with suspicious cytology.[1,2] Although FNAB cytology has high sensitivity and specificity, the rate of specimens that are inadequate for cytological diagnosis (unsatisfactory or nondiagnostic) ranges between 10% and 20% and in another 20% it is not possible to determine with certainty whether the nodule is an adenoma or carcinoma (indeterminate category).[3] Indeterminate cytology may either stem from modest cellular or nuclear changes that may be minimal but indistinguishable from findings of papillary thyroid cancer (PTC), or from the inability to determine capsular and vascular invasion on FNAB specimen findings that are required to define follicular thyroid carcinoma (FTC).[2] Currently, nondiagnostic biopsies are often repeated. For those with indeterminate cytology, surgery with at least a thyroid lobectomy is often recommended to definitively diagnose the nature of these nodules; however, the vast majority prove to be benign. Traditional thyroid FNAB diagnostic capabilities have been expanded by adding immunohistochemical staining for visualization of cancer-associated antigens, measurement of tissue-specific proteins, and most importantly by analyzing DNA cell content.[4] The 2 most promising applications of molecular pathology techniques in thyroid FNAB are cDNA microarray analysis and the determinations of specific gene mutations.

Of all gene alterations identified in thyroid cancer, the B-Raf^{V600E} mutation is the most common and is specifically found in PTC. It has a fundamental role in thyroid tumorigenesis through aberrant activation of the mitogen-activated protein kinase (MAPK) pathway, and is generally correlated with tumor aggressiveness. The detection of B-Raf^{V600E} mutation in thyroid cells is thought to perhaps increase the diagnostic utility of thyroid FNABs, to help predict thyroid malignancy with better specificity, and to potentially guide the extent of initial surgical treatment. Here we review the significance of screening for B-Raf^{V600E} mutation in thyroid FNABs, and discuss possible implications of its identification on the initial surgical treatment of thyroid nodules with PTC cytology.

B-Raf^{V600E} Activation of the MAPK Pathway

Since the initial discovery of B-Raf^{V600E} mutation in human cancer,[5] mutations were identified in approximately 29% to 83% of PTCs, 66% of melanomas, and in a smaller percentage of other tumors, including colonic and ovarian carcinoma and some sarcomas.[6] B-Raf is a member of the Raf family of protein kinases. The Raf gene products are RAS effectors, and regulate the MAPK signaling pathway, which connects extracellular signals to transcriptional regulation.[6] Among the 3 known Raf kinases (A-Raf, B-Raf, and C-Raf), B-Raf is the most potent activator of the MAPK pathway.[7] The gene encodes a cytosolic serine–threonine protein kinase that is also expressed in thyroid follicular cells.[8] B-Raf protein is activated at the membrane level through a complex process that involves multiple phosphorylation events and protein/lipid interactions. It subsequently activates MAPKK (MEK), which then phosphorylates MAPK (ERK).[9,10] Both B-Raf and MAP kinases are dependent on upstream Ras and tyrosine kinase receptor activation.[11–13]

B-Raf^{V600E} is an oncogenic protein with markedly elevated kinase activity that overactivates the MAPK pathway.[5,14,15] There have been more than 40 mutations identified in the B-Raf gene; however, more than 80% of these mutations correspond to a T→A transversion at nucleotide position 1796 that results in the substitution of valine by glutamate at position 600 of the kinase activation segment[5,7,16] (Fig. 1).

Clinicopathological Correlation

B-Raf Mutation in PTC

The B-Raf^{V600E} mutation represents the hallmark of PTC, and to date it has not been identified in medullary

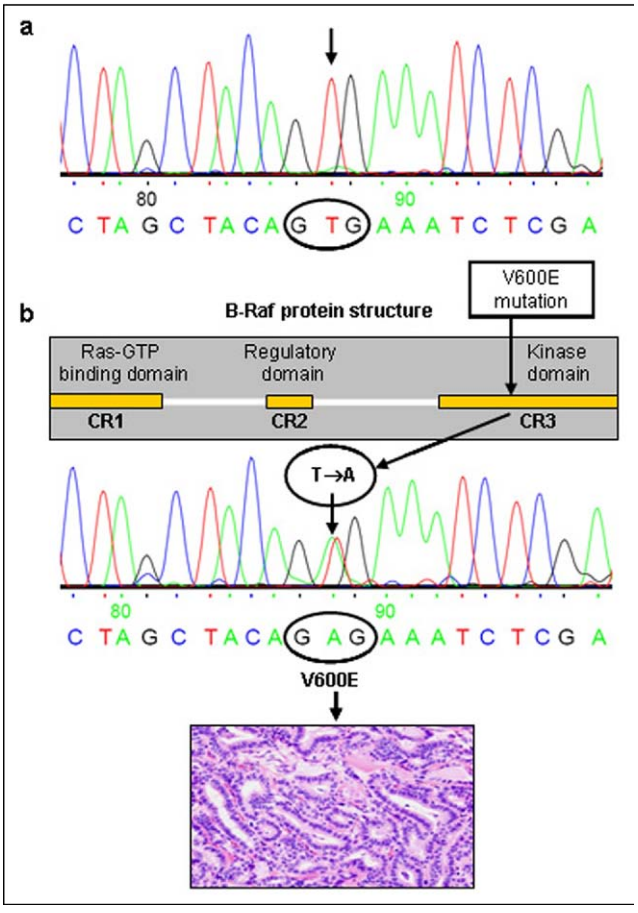

Figure 1 Analysis of B-Raf gene exon-15 by DNA automated sequencing. (A) Electopherogram showing wild-type B-Raf gene (sequence nGTGn at nucleotide 1796) in a human normal thyroid tissue sample. (B) B-Raf gene shows the 3 conserved domains CR1, CR2, and CR3, which are affected by the V600E mutation. The pherogram shows the T1799A (V600E) activating point mutation of the B-Raf gene in a conventional type of human PTC.