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Mutations of the RAS Oncogene Are Found in Follicular Variant Papillary Thyroid Carcinoma

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Gupta N, Dasyam AK, Carty SE, Nikiforova MN, Ohori NP, Armstrong M, Yip L, Lebeau SO, McCoy KL, Coyne C, Stang MT, Johnson J, Ferris RL, Seethala R, Nikiforov YE, Hodak SP. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. J Clin Endocrinol Metab 2013;98:E914-22. Epub March 28, 2013; doi: 10.1210/jc.2012-3396.

SUMMARY

Background

Oncogenic mutations are found in more than half of differentiated thyroid cancers (DTCs). The most common mutation is BRAF V600E. The next most common mutation is in the RAS tyrosine kinase that is located upstream of RAF in the mitogen-activated protein kinase pathway. There are several RAS point mutations, subclassified as NRAS, HRAS, and KRAS. However, these mutations are also found in benign adenomas and less commonly in hyperplastic goiters. This article is a comprehensive clinical study of the largest series to date of tumors harboring RAS mutations that were detected prospectively in thyroid FNA biopsies.

Methods

All aspirated nodules were 1 cm or greater. The point mutations NRAS codon 61, HRAS codon 61, and KRAS codons 12 and 13 were detected using real-time PCR. The mutations were retested in resected specimens.

Results

Between April 2007 and April 2009, a total of 921 patients who underwent thyroid-nodule FNA were evaluated prospectively with a panel of molecular markers. RAS mutations were found in 68 aspirates from 66 patients (7.2%). The identified mutations were NRAS codon 61 in 49 (72%), HRAS codon 61 in 15 (22%), and KRAS codon 12 or 13 in 4 (6%) aspirates. Based on the Bethesda classification for thyroid FNA cytology, 63 of 68 RAS-positive aspirates (93%) had a diagnosis in the indeterminate categories, 3 (4%) were malignant, and 2 (3%) were negative for malignant cells. Of the 63 cytologically indeterminate aspirates, 32 (51%) were classified as follicular neoplasm/suspicious for follicular neoplasm, 22 (35%) as follicular lesion of undetermined significance, and 9 (14%) as suspicious for malignant cells.

Sixty-three nodules of RAS-positive patients were resected, and cancer was confirmed in 52 specimens (83%) from 50 patients. The RAS-positive cancers included 46 follicular variant PTC, 4 follicular thyroid carcinomas, 1 medullary thyroid carcinoma, and 1 anaplastic thyroid cancer. Microdissections of 4 DTCs with mutation analysis of three separate areas of each tumor showed the same mutation, indicating that they were clonal neoplasms.

Of the 63 RAS-positive aspirates, 11 nodules (17%) were found to be histologically benign; 7 of these nodules were follicular adenomas with microfollicular architecture and the other 4 were hyperplastic nodules.

Only one third of the RAS-positive malignant nodules had at least one ultrasonographic feature associated with cancer.

Conclusions

Most RAS-positive thyroid cancers have indeterminate cytology, lack suspicious ultrasound features, and are histologically low-grade follicular variant PTC.

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ANALYSIS AND COMMENTARY

Although this study was relegated to the electronic (Web) pages of the Journal of Clinical Endocrinology and Metabolism, suggesting that it was of less clinical significance than papers in the print version, I believe that it has significant clinical importance. The study confirms that RAS mutations in FNA specimens are strongly indicative of thyroid cancer (1). The vast majority of the cancers were follicular variant PTC, a tumor that is difficult to diagnose accurately on FNA cytology. The finding of homogeneous distribution of the specific RAS mutation throughout the DTC indicates that these lesions are clonal neoplasms, suggesting that the RAS mutation is an early and crucial event in thyroid neoplasia. However, the fact that these mutations are also found in benign adenomas and hyperplasia diminishes their impact on being solely responsible for oncogenesis.

The encapsulated follicular variant of PTC with the RAS mutations that predominated in this series tends to have a much better prognosis than classical PTC, especially those that harbor the BRAF mutation (2). Because only 7.2% of the nodules had RAS mutations, one can argue that it may not be cost-effective to screen for it, even though it is much more prevalent than the BRAF mutation (1). The argument for screening for the BRAF mutation is that it has an ominous prognosis; finding it can be a basis for more aggressive therapy. However, BRAF is found in the classical PTC that can be diagnosed frequently by positive ultrasound findings, such as microcalcifications. Because ultrasonography is usually not suggestive of malignancy in nodules with the RAS mutations, as found in this series, screening for the mutation can be very helpful to indicate whether thyroidectomy is justified.

References

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