BRAF MUTATION GUIDES THERAPY OF NODULES WHEN CYTOPATHOLOGY IS INDETERMINATE

Kim SK, Hwang TS, Yoo YB, Han HS, Kim DL, Song KH, Lim SD, Kim WS, Paik NS. **Surgical results of thyroid nodules according to a management guideline based on the BRAFV600E mutation status.** J Clin Endocrinol Metab. January 14, 2011 [Epub ahead of print]. doi:10.1210/jc.2010-1082

SUMMARY

BACKGROUND AND METHODS

In Korea, more than 90% of well-differentiated thyroid cancer is papillary, and the BRAFV600E mutation is found in more than 80%, higher percentages than what are found in many Western countries. Over the 2-year period beginning in March 2007, the cytopathology in 865 fine-needle aspiration biopsies (FNAB) of thyroid nodules was prospectively analyzed at Konkuk University in Seoul using the 2008 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Guidelines. The cover slips were then removed from the slides and "atypical cells of interest" were scraped and DNA was extracted and analyzed for the BRAFV600E mutation using polymerase chain reaction (PCR) with a biotinylated primer, purification with streptavidin–agarose and pyrosequencing.

RESULTS

In the 504 FNABs that were read as being "benign," no BRAFV600E mutants were found. The mutation was found in 32% of the 141 samples read as "atypical cells of undetermined significance" (ACUS), in 85% of the 54 samples read as "suspicious for malignancy," in 92% of the 140 samples read as "malignant," and in 10% of the 10 samples read as "suspicious for follicular neoplasm." BRAF status could not be assessed on 16 FNABs with insufficient material for cytopathologic assessment.

Surgery was advised in all cases in which FNAB cytology was read as suspicious for malignancy or malignant. Papillary thyroid carcinoma was found in all who actually underwent surgery, whether or not the BRAFV600E mutation was present.

In the cases read as "ACUS," surgery was recommended for all 45 cases in which BRAFV600E mutation appeared. Surgery was actually performed on 30: 29 proved to be papillary thyroid carcinoma, while 1 turned out to have nodular hyperplasia, a false positive. Surgery was also performed on 12 patients whose FNAB was read as "ACUS" but did not have the BRAFV600E mutation, because ultrasonography showed they were over 50% solid and over 2 cm in diameter, or were of any size but had suspicious features such as microcalcifications, irregular margins, hypoechogenicity, or abnormal neck lymphadenopathy. Eight turned out to be nodular hyperplasia, 1 was a follicular adenoma, 2 were papillary carcinomas and 1 was a follicular carcinoma. Thus, of 30 ACUS nodules with the BRAFV600E mutation, 29 had papillary carcinoma. In the 12 cases of ACUS that did not have a mutation in BRAF but had worrisome clinical features, 3 were malignant.

In all 10 cases read as "suspicious for follicular neoplasm," surgery was recommended. Of the 9 who did not have the BRAFV600E mutation, 3 had follicular carcinoma, 3 had nodular hyperplasia, 1 had a follicular adenoma, and 2 refused surgery.

CONCLUSIONS

Demonstrating that the BRAFV600E mutation is present in material from an FNAB that has been read as "ACUS" appears to be helpful in deciding whether to send a patient for surgery, even in the absence of troublesome clinical features.

COMMENTARY

The distribution of thyroid cancers in Korea is different from what is found in many Western countries, but if this method of analyzing FNABs for the BRAFV600E mutation can be adopted without too much difficulty and the results confirmed in places where a higher percentage of samples are read as "atypical cells of undetermined significance," it could simplify the preoperative evaluation and obviate the need to evaluate frozen sections intraoperatively in such cases. Methodologic problems, including "oversensitivity" can arise when analyzing DNA sequences in FNAB material. A report from another group in Seoul (1) looked for the BRAFV600E mutation in FNAB material left over after cytology slides were made. A multiplex PCR with a long primer interrupted by a series of 5-deoxyinosine residues was used on the FNAB material, while direct DNA sequencing was performed on DNA scraped from paraffin sections of surgical samples from 279 patients. The DNA analysis on leftover FNAB material detected 5 false positive BRAFV600E mutations, as compared with the direct DNA sequence data obtained from the paraffin material. Both papers confirm the finding of others (including the paper of Proietti, that was reviewed in the February 2011 issue of Clinical Thyroidology), namely that the BRAFV600E mutation is uncommon in predominantly follicular lesions (2).

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References

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