

Primary Thyroid Lymphomas May Have BRAF Mutations That Suggest a Diagnosis of Thyroid Cancer

Jerome M. Hershman

Aggarwal N, Swerdlow SH, Kelly LM, Ogilvie JB, Nikiforova MN, Sathanoori M, Nikiforov YE. Thyroid carcinoma-associated genetic mutations also occur in thyroid lymphomas. *Mod Pathol* 2012;25:1203-11. Epub May 11, 2012.

SUMMARY ●●●●●●●●●●●●●●●●●●●●●●●●

Background

The BRAF V600E oncogenic mutation is found in 40% to 45% of papillary thyroid carcinomas (PTCs). It activates the mitogen-activated protein kinase (MAPK) signaling pathway. Because this mutation can be detected in thyroid FNA aspirates, screening for it has been advocated (1). The BRAF V600E mutation is also found in anaplastic or poorly differentiated thyroid cancers that have a papillary component. Primary thyroid lymphomas are relatively rare and frequently present as rapidly growing masses in the thyroid gland. The present report shows that a significant number of thyroid lymphomas have BRAF mutations, although only the index case in this series had the BRAF V600E mutation.

Methods

Archived pathology specimens of 33 primary thyroid B-cell lymphomas were studied for mutations in the MAPK signaling pathway. Microdissection of the specimens was performed; the DNA was isolated and studied by real-time PCR. The hot spots in BRAF codons were amplified and sequenced. The DNA was also studied for mutations in NRAS, HRAS, and KRAS.

Results

In a patient with a thyroid mass, FNA was used to diagnose both carcinoma and lymphoma. Molecular

analysis of the aspirate was positive for the BRAF V600E mutation. After excision, the tumor was found to be a diffuse large-B-cell lymphoma, and there was no PTC in the thyroid. This led to the study of 33 thyroid lymphomas that came from 28 women and 5 men with a mean age of 65 years; 25 were diffuse large-B-cell lymphomas, 6 were extranodal marginal-zone lymphomas, and 2 were follicular lymphomas. Eight of the 33 lymphomas were positive for one of the studied mutations. There were six BRAF mutations, including the BRAF V600E mutation found in the index case, three D594G mutations, and two K601N mutations. In addition, there were 2 NRAS mutations, Q61K and Q61H. All of these mutations were identified in the diffuse large-B-cell lymphomas. None of the cases had mutations in KRAS or HRAS.

The patients were treated with surgery, radiation, and chemotherapy. Eleven of the 33 died from the lymphoma. There was no difference in survival between the group with and that without mutations.

Conclusions

The data show that, when a BRAF or NRAS mutation is found in a thyroid aspirate, the differential diagnosis should include primary thyroid lymphoma in addition to thyroid carcinoma.

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ANALYSIS AND COMMENTARY ● ● ● ● ●

The authors state that this is the first report of BRAF and NRAS mutations in primary thyroid lymphomas. Lee et al. reported that 4 of 67 diffuse large-B-cell lymphomas found in nonthyroid sites had BRAF mutations, but they were not in codon 600 (2). At the most recent ATA meeting in Quebec, Jayakumar and Shifrin reported a patient with thyroid lymphoma that had the BRAF V600E mutation (Program of the 82nd Annual Meeting of the American Thyroid Association, page 194). Last year we performed an FNA of a 1.9-cm thyroid nodule in a patient who had been treated 2 years earlier for diffuse large-B-cell lymphoma and was considered disease-free. The aspirate yielded only atypical lymphoid cells and was positive for the BRAF V600E mutation.

The BRAF V600E mutation is found in many cancers besides PTC: about half of cases of metastatic melanoma, a small fraction of colon cancers, and nearly all of hairy-cell leukemias, among others. The NRAS Q61K mutation identified in this study is commonly seen in follicular thyroid cancer (3). As mutation analysis is applied more commonly to thyroid lesions, one must be aware that nonthyroid neoplasms may harbor activating mutations of the MAPK pathway, even when the lesions reside in the thyroid area.

Primary thyroid lymphoma is usually found in patients with a background of Hashimoto's thyroiditis (4). Unfortunately, the current report did not provide data in this regard.

References

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