RET/PTC REARRANGEMENT MAY DETERMINE RAPID GROWTH OF BENIGN THYROID NODULES

Sapio MR, Guerra A, Marotta V, Campanile E, Formisano R, Deandrea M, Motta M, Limone PP, Fenzi G, Rossi G, Vitale M. **High growth rate of benign thyroid nodules bearing RET/PTC rearrangements.** J Clin Endocrinol Metab 2011;96:E916-9. Epub March 16, 2011.

SUMMARY

BACKGROUND

The most characteristic clinical hallmark of a malignant thyroid nodule is its rapid growth. However, even benign thyroid nodules may attain a considerable size within a short period. Fine-needle aspiration cytology (FNAC) and ultrasonography are the most widely used techniques to distinguish malignant from benign nodules. Much effort has been invested in unraveling the molecular signaling pathways that may help promote malignant growth, but only a few studies are available on the mechanisms that enhance the growth rate of benign nodules, particularly the so-called cold nodules.

In thyroid cancers, one of the known growth-promoting factors is a constitutive activation of chimeric cytoplasmic kinases that result from a rearrangement of the RET/PTC genes. This rearrangement is by itself not a marker for malignancy, since it also occurs in benign nodules. The authors performed a prospective multicenter study to determine whether the RET/PTC rearrangement may be a mechanism that promotes the growth of a particular subset of benign nodules.

METHODS

A total of 125 patients were included in this Italian study. One of the inclusion criteria was a nodular diameter of 10 mm or more, the other being the results of FNAC, which were required to be consistent with a Thy2 colloid nodule (according to the criteria of the British Thyroid Association). When more than one nodule was present, only the largest one was considered. The size of the nodules was measured by ultrasonography. Patients on suppressive thyrotropin therapy and/or those with scintigraphic evidence of partial thyroid autonomy were excluded. FNAC was evaluated by three qualified pathologists, and the remainder of the preparation was used for RNA extraction that was further reverse-transcribed by polymerase chain reaction (RT-PCR). As a test of confidence, the PCR product of four nodules was sequenced and proved to be the PCR-amplified product corresponding to the RET/PTC modification of the cDNA. Ultrasound examination was repeated at 6 months and then at yearly intervals.

RESULTS

In 19 (15%) of 125 patients a rearrangement could be identified. The mean follow-up period was 31 months for RET/PTC-positive and 37 months for RET/PTC-negative nodules. In the group of RET/PTC-positive nodules, three cases had to be excluded because of rapid growth justifying early thyroidectomy. The number of nodules that were finally surgically removed was not indicated. During the observation period, the volume of RET/PTC-negative nodules increased from 2.61 to 3.18 ml and in the RET/PTC-positive cases from 3.04 to 5.04 ml. In both groups, the increase was highly significant. The increase in the RET/PTC-positive nodules was clearly and significantly higher than in the RET/PTC-negative ones. Expressed as a percentage growth rate per month, the RET/PTC-positive nodules again increased significantly faster than the negative ones.

CONCLUSIONS

The results of RT-PCR assay performed on material obtained from thyroid nodules by FNAC—a highly demanding technique (1)—lend support to the assumption that a RET/PTC rearrangement might be one of the important molecular mechanisms contributing to enhanced cell replication in rapidly growing benign nodules. The results also demonstrate that by itself the rearrangement is not carcinogenic, since thyroid nodules harboring this mutation do not acquire an aggressive nature. The authors do not suggest that their technique should play a role in the diagnostic workup of thyroid nodules. This cautious conclusion is based on the evidence that many RET/PCR- negative nodules were also found to have a rather high growth rate, thus indicating that other growth factors must be involved in promoting the growth of benign as well as malignant thyroid nodules.

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COMMENTARY

In this cohort, many RET/PTC-positive but also some RET/PC-negative nodules showed considerable growth over a relatively short period of observation. This is rather unexpected, since most thyroid nodules are reported to grow rather slowly or even to remain at least temporarily stable. Possibly, moderate iodine deficiency that is still prevalent in Italy, could represent a additional goitrogenic stimulus. Nevertheless, the mean growth rate of all nodules harboring the RET/PTC rearrangement was unequivocally higher than in the negative nodules. The results certainly stress the importance of the RET/PTC rearrangement for growth rate, but they also clearly suggest the presence of other unknown growth-promoting mechanisms. The heterogeneity of the results is in no way surprising, given the notorious intercellular functional heterogeneity among thyrocytes. The authors consider as possible explanations individually differing intensity of RET/PTC expression.

The authors cautiously consider the possibility that the RET/PTC rearrangement detected on FNAC could help clinicians to choose surgery as the first-line therapeutic approach in a given thyroid nodule. However, most clinicians would probably advise surgical treatment to any patient with a steadily growing thyroid nodule irrespective of whether or not RET/PTC rearrangement was present.

In summary, this careful work adds a valuable brick to the ultimate construction of a multistory building that represents the intricate network of growth-promoting mechanisms in benign tumors.

— Albert G. Burger, MD

REFERENCE

1. Nikiforova MN, Nikiforov YE. Molecular diagnostics and predictors in thyroid cancer. Thyroid 2009;19:1351-61.