Letters to the Editor


The article on RET/PTC activation in thyroid tumors published by Tallini et al. (1) reports some very interesting data that fit with most of the results obtained by us using a different methodology (2).

Using immunohistochemistry and reverse transcription-PCR, Tallini et al. (1) studied a large series of thyroid tumors and confirmed the restricted association between RET/PTC rearrangements and the papillary histotype, as well as the apparent inability of papillary tumors harboring RET/PTC rearrangements to progress to less differentiated forms. Furthermore, in the series of Tallini et al. (1) RET/PTC rearrangements seem to be associated with the classic form of papillary thyroid carcinoma.

Using a Southern blot-based strategy to study a series of 33 clinically evident papillary carcinomas, we also found a higher frequency of RET/PTC rearrangements in the classic type of papillary carcinoma (87.5% of the rearranged papillary carcinomas) than in the follicular variant of papillary carcinoma (12.5%; Ref. 2). As in the study of Tallini et al., we did not discover any significant relationship between RET/PTC and the clinicopathological parameters classically associated with poor prognosis (large size, extrathyroidal extension, and metastases). Finally, we observed a suggestively ($P = 0.1$) lower proliferative rate in RET-rearranged papillary carcinomas (2); this finding fits with the association between RET/PTC rearrangement and papillary microcarcinoma (3) as well as with the apparent limited growth potential of RET/PTC transformed cells (4).

At variance with the study of Tallini et al. (1), the mean age of the patients with tumors displaying RET/PTC rearrangement in our series (28 ± 9 years; median, 30 years) was significantly ($P = 0.005$) lower than that of the patients harboring cases that did not present rearrangement (45 ± 15 years; median, 44 years). A similar association between RET/PTC rearrangement and young age of the patients had been previously reported by other groups (5, 6).

Our series did not include papillary microcarcinoma, which—apart from being associated with RET/PTC—seem to occur, at least in some series, in older patients. We wonder whether the exclusion of papillary microcarcinomas from the series of Tallini et al. (1) will disclose an association between RET/PTC rearrangements and young age. In any case, it would be interesting to verify whether there is any relationship between the patients’ age and the different types of RET rearrangement (RET/PTC1, RET/PTC2, or RET/PTC3).

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References

Reply

We are grateful to Drs. Soares and Sobrinho-Simões for their interest in our article. Independent of the technique used to identify the Ret rearrangements, both their series (1) and ours (2) show that Ret/PTC activation is more commonly detected in tumors with a predominantly papillary architecture. Furthermore, findings in both of the series [lack of correlation with clinicopathological markers of increased morbidity (1, 2), the failure to identify Ret/PTC in poorly differentiated and anaplastic thyroid carcinomas (2), and a relatively lower proliferation rate of the Ret/PTC-positive tumors (1)] point to a limited role for Ret/PTC in the development of aggressive forms of thyroid cancer. Similar findings (that is, the association with papillary architecture and lack of correlation with clinicopathological markers of increased morbidity) have also been recently reported using in situ hybridization to detect Ret rearrangement (3). We find this convergence of results very reassuring in light of the wide variation in the prevalence of Ret oncogene activation in thyroid carcinomas (4, 5). Although a well-differentiated papillary carcinoma component was clearly identifiable in only very few of the poorly differentiated and anaplastic tumors analyzed in our study (2), the general impression that Ret/PTC may be weak compared with other oncogenes is also supported by Ret/PTC1 transgenic mouse models. In fact, Ret/PTC1 transgenic mice develop thyroid nodules morpho-
logically similar to papillary carcinomas, which lack poorly differentiated or undifferentiated foci and do not metastasize (6, 7). Indeed, their limited growth potential justifies the comparison with bonsai trees suggested by Soares and colleagues (1). However, transgenic mice carrying other rearranged forms of Ret such as Ret/PTC3 have recently been developed and are associated with a more aggressive tumor phenotype, including competence for lymph node metastases (8).

In their letter, Drs. Soares and Sobrinho-Simões note how, at variance with our study, Ret/PTC was more frequently detected in papillary carcinomas occurring in young patients. They speculate whether the different relationship between Ret/PTC and the patient age at diagnosis when seen in their study and ours (1, 2) may be due to the inclusion of the papillary microcarcinomas in our series. In fact, as anticipated by Drs. Soares and Sobrinho-Simões, a higher proportion (45.6%) of the tumors measuring 1 cm or less (that is, papillary microcarcinomas) were positive for Ret/PTC compared with the larger papillary tumors (38.4%). Also, papillary microcarcinomas tended to occur in an older age group; the patients’ average age was 49 ± 14 (mean ± SD) compared with an average age for the larger tumors of 41 ± 16 (mean ± SD). However, exclusion of the papillary microcarcinoma (55 of the 201 cases analyzed) from our series fails to disclose any statistically significant association between Ret/PTC and young age. Nevertheless, it reveals a distribution of the Ret-rearranged papillary carcinomas that overlaps that reported by Dr. Soares and colleagues (1). Exclusion of the microcarcinoma from our series, in fact, discloses a peak for the Ret/PTC-rearranged tumors in the 4th decade (48.6% positive cases), a relative decrease in the Ret-rearranged papillary carcinomas in the 5th, 6th, and 7th decades, and a possible second peak in the oldest age group (patients aged 70 years or older), in which the proportion of Ret-rearranged cases was 50.0%. This distribution is even more apparent after the exclusion not only of the microcarcinomas but also of the male patients. A high prevalence of Ret/PTC-rearranged papillary carcinomas in young females is also apparent in the study of Soares and colleagues (1) in which Ret rearrangement was detected in 6 of 9 tumors from female patients in their 30s, a proportion which is similar to that found in the same group of patients in our study (13 of 26 tumors or 50.0%). In addition, our study (2) shows that the proportion of Ret-rearranged papillary carcinomas in male patients increases until the 6th decade of life even if microcarcinomas are excluded, thus supporting the putative influence of gender (9) on the role played by Ret/PTC in the development of thyroid tumors. Concerning a possible relationship between the patients’ age and the different types of Ret rearrangement: the parallel analysis of 25 samples by reverse transcription-PCR supports the immunohistochemical results (2) but fails to disclose any association between the type of Ret rearrangement (Ret/PTC1, Ret/PTC2, Ret/PTC3) and the sex or age of the patient.

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References

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