Letters to the Editor

CORRESPONDENCE RE: CAMESELLE-TEIJEIRO J, CHAN JKC: CRIBRIFORM-MORULAR VARIANT OF PAPILLARY CARCINOMA: A DISTINCTIVE VARIANT REPRESENTING THE SPORADIC COUNTERPART OF FAMILIAL ADENOMATOUS POLYPOSIS–ASSOCIATED THYROID CARCINOMA? MOD PATHOL 1999;12:400–11.

To the Editor: Camaselle-Teijeiro and Chan have recently described four personal cases and reviewed five other similar cases reported in the literature of an unusual sporadic thyroid tumor that shares the morphologic features of a distinctive follicular cell neoplasm (1), namely the cribriform variant of papillary carcinoma, that has previously been proposed as a feasible indicator of familial adenomatous polyposis (FAP) (2–6). They put together small tumors (12 to 15 mm) and large thyroid tumors (40 to 50 mm) and tried to define the morphologic and immunohistochemical features common to or typical of this variant. Unfortunately, they did not perform any genetic analysis concerning the molecular hallmark of the papillary histotype, namely ret/PTC translocation (7). Finally, on the basis of a medium-term follow-up, they concluded that "the behavior of this variant, representing the sporadic counterpart of FAP-associated thyroid carcinoma, seems to be similar to that of conventional papillary carcinoma" (1–7).

On the basis of our extensive analysis of 15 personal cases of FAP-associated thyroid carcinomas (TCs) (6), all of which had molecular genetic analysis, and on the review of the literature concerning TC in patients with FAP (6,7), we would like to make some comments on this subjects.

TC in patients with FAP has a striking predominance for females (female-to-male ratio, 17:1) (6–10) and is usually diagnosed earlier than sporadic tumors (10). In siblings of an affected FAP proband, screened for TC, TC shows a peculiar genetic pattern: very high incidence of ret/PTC mutations, lack of loss of heterozygosity for APC (the suppressor gene responsible for FAP) in the thyroid tumoral tissue, and good prognosis (7–10). Most of the 110 patients with FAP-associated TC reported in the literature did not produce distant metastases, and the patients had a mean survival of more than 15 years without recurrence. We suspect that early diagnosis, as a result of intensive screening in patients with multitumoral diseases (9,10), could be responsible, at least partly, for histologic and molecular features, which are described as typical of FAP-associated TC. In our series (5,10), no patient had a tumor larger than 2 cm. All of them had encapsulated tumors. However, as pointed out by other authors (9), these tumors, which usually show ret/PTC activation as ret/PTC1 are associated with a good prognosis and do not show p53 mutation, may acquire with time the likely more malignant ret/PTC3 mutation in concomitance with p53 activation (9,10).

It is well known from liver carcinogenesis that in nodules increasing in size from 15 to 30 mm, clonal selection occurs and a different histologic pattern usually develops, close to the previous one. Accordingly, in a kindred with the same APC germ-line mutation, tumors that are smaller than 1 cm in diameter will show different histologic aspects from tumors that are larger than 2 (or 4) cm, occurring in other members of the same family. In addition, even in TCs of the same size, occurring in members of the same kindred, with the same germ-line mutation of the APC gene, a wide variety of histologic aspects have been found. In particular, two siblings showed focally or extensively a cribriform pattern, whereas it was completely absent in the third sibling (5). Therefore, even if the cribriform patterns are unusually more frequent in FAP-associated TCs, this must not be considered as a rule. This means that (1) solid, or typical, papillary patterns occurring in a patient with FAP cannot be dismissed as "not FAP-related" TC and (2) sporadic tumors similar in morphology to those described in FAP do not necessarily share the same biologic behavior (9,10).

We agree with the authors' conclusion that the cribriform-morular variant of TC must not be mistaken for other aggressive thyroid neoplasms, such as the tall cell variant of TC or poorly differentiated TC. However, we suggest a word of caution before suggesting that some histologic patterns are typical of FAP-associated TC and "their sporadic counterparts." More information from a molecular point of view is required, in particular, concerning the biologic significance of the activation of the various ret/PTC isoforms, the role of APC and p53 in thyroid carcinogenesis, and the mutual relationships among oncogenes and tumor suppressor genes, before a precise statement can be achieved.

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In reply: We thank Drs. Cetta *et al.* for their interest in our article (1) and comments. As Harach *et al.* (2) concluded, the thyroid carcinomas developing in patients with familial adenomatous polyposis (FAP) had a peculiar histologic appearance, and its microscopic features might provide the first indicator for an unsuspected, underlying FAP syndrome. Cetta *et al.* proposed that early diagnosis of thyroid carcinoma in FAP patients could be responsible, at least partly, for histologic and molecular features described as typical of FAP-associated thyroid carcinoma. However, given the association between the unusual morphologic pattern of this variant of thyroid carcinoma in patients with FAP syndrome reported by several authors (3–6), the low prevalence of *APC* gene mutations in sporadic thyroid neoplasms (7), and the fact that somatic *APC* gene mutations are not found in the typical sporadic papillary thyroid carcinoma (8), we feel that, *APC* gene mutations must play some role in the unusual morphologic features of FAP-associated thyroid carcinoma. In our opinion, various interactions among oncogenes and tumor suppressor genes, as well as clonal selection, could justify the existence of thyroid tumors, without this peculiar histologic pattern of papillary thyroid carcinoma (PTC) in patients with FAP syndrome. For the same reason, we agree with Cetta *et al.*, that usual and/or other patterns of growth in papillary carcinomas do not reliably permit us to exclude FAP syndrome.

In our article (1), we did not imply that these sporadic tumors are biologically identical to FAP-associated thyroid carcinoma. Thus we were cautious enough to coin the term "cribriform-morular variant" instead of calling it "FAP-associated thyroid carcinoma." We also put a question mark in the title to indicate uncertainty. Nonetheless, the sporadic tumors that we describe are indeed morphologically indistinguishable from most of the papillary carcinomas that arise in the setting of FAP. Because we were familiar with many of these distinctive microscopic features, we were recently able to identify a case of cribriform-morular variant of PTC with somatic but no germ-line mutation in exon 15 (codon 1309) of the *APC* gene (unpublished observations). The patient, a 27-year-old woman, presented no congenital hypertrophy of the retinal pigment epithelium, nor had she any personal data or family history of FAP. In our opinion, this case of cribriform-morular variant of PTC constitutes additional evidence of the relationship between the morphologic pattern of cribriform-morular variant and the *APC* gene mutations and the existence of a sporadic counterpart of FAP-associated thyroid carcinoma. Cetta *et al.* (4) have apparently underemphasized the role of the *APC* gene in the genesis of the FAP-associated thyroid carcinoma by saying that there is lack of loss of heterozygosity for APC in the thyroid tumoral tissue. However, in some studies, there is somatic mutation of the *APC* gene in such tumors, in addition to the presence of germline mutation (6, 9).

However, we have two main messages in our article (1). First, the most important reason to recognize this variant is to ensure that it is not mistaken for other aggressive thyroid neoplasms, such as the tall cell variant of PTC, columnar cell carci-

noma, or poorly differentiated thyroid carcinoma. To cite an example, we think that the conflicting data (sex and biologic course) in the Armed Forces Institute of Pathology series presented by Wening *et al.* (10) can be explained by the fact that some cases of columnar cell carcinoma are actually cases of the cribriform-morular variant of PTC. Second, whenever a cribriform-morular variant of PTC is encountered, the clinician should be alerted to exclude FAP.

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