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Thyroid Cancer in Patients with Familial Adenomatous Polyposis

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Abstract. The association between thyroid cancer and familial adenomatous polyposis (FAP), albeit rare, is well known. It has been suggested that the thyroid tumors have unique histologic characteristics and may be follicular in origin. Because of their rarity, treatment and long-term prognosis are uncertain. Twelve such patients (prevalence 399/100,000) seen during 1949–1995 were retrospectively reviewed. Histology was independently re-reviewed by two pathologists. There were 11 female patients (two sisters) and 1 male patient, with a mean age of 28 years (range 15–61 years). Eight patients (66%) had multicentric tumors and five (42%) bilateral disease. Average tumor diameter was 1.8 cm (range 0.2–5.0 cm). Regional nodal metastases were present in two patients. All 12 thyroid cancers in this series were papillary. The one male patient demonstrated "typical" histology with variable papillary and follicular architecture, whereas the 11 female patients had tumors with unusual histology as described by Harach. Five patients (41%) were treated by total thyroidectomy, five with near-total thyroidectomy, and two with lobectomy alone. Mean follow-up was 142 months (range 7 months to 30 years). Regional recurrent disease occurred in two patients, one of whom died of the disease. The 5- and 20-year survivals were 90% and 77%, respectively. The results indicated that all tumors in this study were papillary, although atypical histology was encountered in 91%. The mean age (28 years) is younger than that of patients with sporadic disease. Multicentricity and bilateral disease are common. In view of this finding, total thyroidectomy should be strongly considered. Long-term prognosis is excellent. The finding of unusual histology in a young patient with papillary thyroid carcinoma should arouse the suspicion of FAP.

Gardner was the first in 1951 [1] to bring attention to the extracolorectal manifestations of familial adenomatous polyposis (FAP), commonly referred to as Gardner syndrome. He described, in this sentinel report, the triad of FAP, osteomas, and soft-tissue tumors (epidermoid cysts and subcutaneous fibromas). The protean manifestations of FAP are today well established and may include, in addition to the originally described triad, desmoid tumors, duodenal or periampullary tumors, retinal pigmentation, dental abnormalities (most commonly supernumerary teeth), hepatoblastomas, and malignant central nervous system tumors (Turcot syndrome) [2].

In 1968 Camiel et al. [3] for the first time suggested the relation of FAP with thyroid carcinoma. They reported the presence of papillary thyroid carcinoma in two young sisters with classic FAP. In this report the authors reflect that the first to draw attention to this possible association may well have been Crail [4], who in 1949 presented a single case report of a patient with primary malignancies arising in the rectum, brain, and thyroid gland.

During the ensuing decades, a number of excellent reports have further analyzed this interesting association [2, 5–9]. These reports have tried to: (1) answer the question whether there is, in fact, an increased incidence of thyroid carcinoma in FAP patients [5–10]; (2) detail the clinical course and suggest appropriate treatment of the thyroid malignancy [6, 10, 11]; and (3) detail the histopathology of thyroid cancer per se [8, 12]. The latter report suggested that the histology encountered in such thyroid tumors was indeed unique in FAP patients, being atypical for the classic, more commonly encountered papillary and follicular carcinomas; it also noted that the tumors were most often multicentric and bilateral and tended to occur predominantly in young females. The authors [12] suggested that these atypical histologic findings should alert the physician to screen such patients with thyroid carcinoma for the possible presence of FAP.

Because most reports in the literature to date have been single case reports, we initiated this retrospective study by combining databases from various FAP registries and by independently re-reviewing all histology. The objectives of this study were to: (1) detail the clinical course and treatment of patients with FAP and thyroid carcinoma; (2) delineate the temporal relation between these two entities; (3) describe accurately the histopathologic aspects of the thyroid malignancy; (4) ascertain, if possible, if there is an increased incidence of thyroid carcinoma in patients with FAP; and (5) suggest appropriate treatment of, and screening for, thyroid carcinoma in patients with FAP.

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Materials and Methods

The FAP registries from the Mayo Clinic and the Cleveland Clinic for the years 1940–1995 were reviewed to identify patients with thyroid carcinoma. In addition, a recent patient with FAP from the University of Minnesota in Minneapolis who underwent thyroidectomy was included in the study. Only those patients for whom histologic slides or paraffin-embedded blocks were available for study were included. All histologic slides were reviewed by J.R.G. of the Mayo Clinic and E.D.W. of Cambridge University (UK).

Results

Twelve patients fulfilled the study criteria (seven at the Mayo Clinic, four at the Cleveland Clinic, one at the University of Minnesota).

Age/Sex

There were 11 female patients (two of whom were sisters) (mean age 25.5 years, range 15–38 years) and a single 61-year-old male patient. The average age at the time of FAP diagnosis was 24.3 years (15–36 years), and the average age at the time of thyroid cancer diagnosis was 24.9 years (15–38 years).

Temporal Relation to FAP

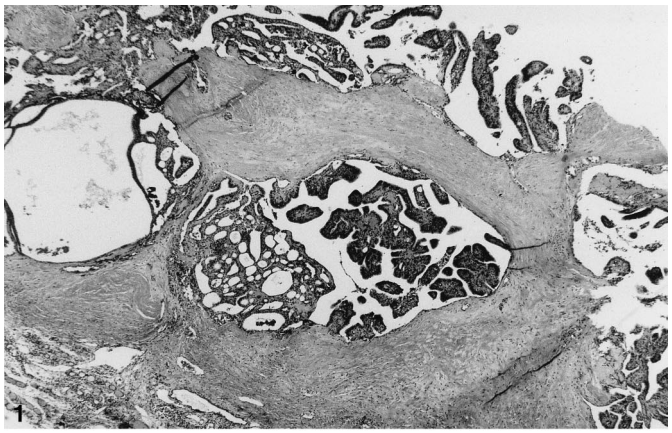
Four (33%) of the patients had a diagnosis of thyroid cancer before the diagnosis of FAP, the mean number of years between diagnoses being 5.25 years (1–13 years). Five (42%) of the patients had the FAP diagnosis prior to the diagnosis of thyroid cancer, the mean number of years between diagnoses being 7.6 years (1–12 years). Three (25%) of the patients had the two diagnoses made simultaneously.

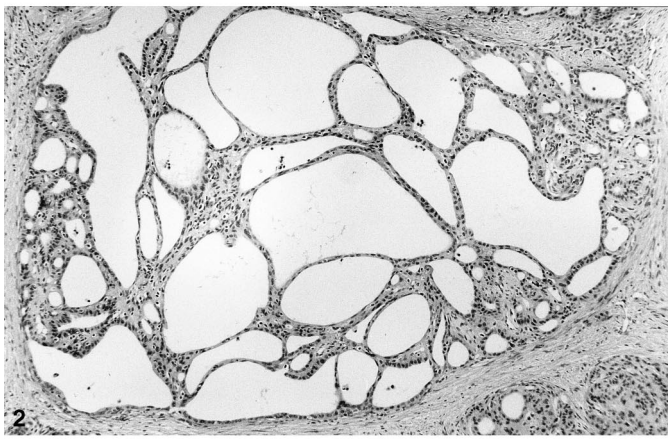
Pathology

Material from thyroidectomies carried out on 12 patients with FAP were available for pathologic re-examination (by J.R.G. and E.D.W.). In one case (the 61-year-old man) there were features of a multinodular goiter with a small focus of well-differentiated papillary thyroid cancer with usual histology. The remaining 11 cases had features resembling those described in a recent small series of thyroid carcinomas associated with FAP [12]. In contrast to the 61-year-old man, these 11 patients were female with an average age of 23.5 years.

The material available for study consisted of stained slides from 10 patients and paraffin blocks from 2 patients. Eight patients (66%) had multicentric papillary cancer with a mean tumor diameter of 1.8 cm (range 0.2–5.0 cm). Bilateral tumors occurred in five patients (42%) and regional nodal metastases in two (17%). Both of the latter two patients also had bilateral multicentric disease. One, a 38-year-old woman with three tumors (2.0, 3.0, and 5.0 cm in diameter), had extensive local invasion, and a laryngectomy specimen from this patient showed invasion around the cartilage. The other patient with nodal disease, a 31-year-old woman, had two tumors (1.2 and 1.5 cm in diameter).

Pathologic review of all lesions showed that most had a fibrous capsule, bands of fibrosis, and areas of stromal sclerosis within the tumor. Capsular or vascular invasion, or both, was evident in half of the sections examined. The tumors showed a mixture of architectural patterns (Fig. 1) with cribriform (Fig. 2), papillary (Fig. 3), glandular, and solid areas each occurring in more than half the lesions. Whorls of cells resembling squamous cell nests but lacking keratinization were found in one-third of the lesions





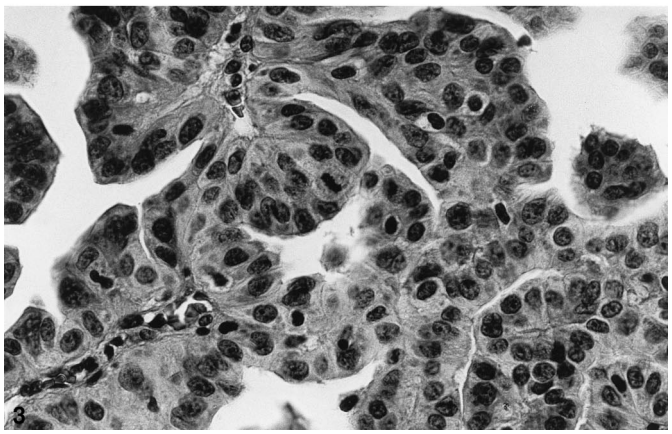


Fig. 1. Low-power view of a thyroid tumor showing an area with a part papillary and part cribriform pattern with dense fibrosis.

Fig. 2. Thyroid tumor showing a cribriform pattern, with distended lumens separated by back-to-back epithelium. No colloid is present.

Fig. 3. High-power view of a papillary area. Note the tall cells with irregular oval, occasionally grooved nuclei. There is a single mitosis.

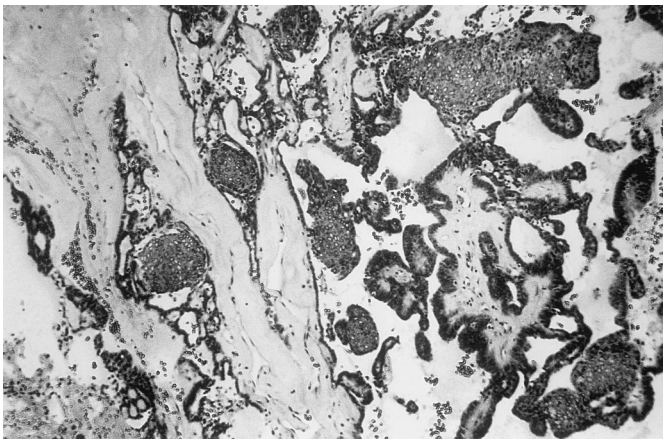


Fig. 4. Glandular spaces with a few papillae with columnar epithelium and some scattered solid foci of squamoid epithelium.

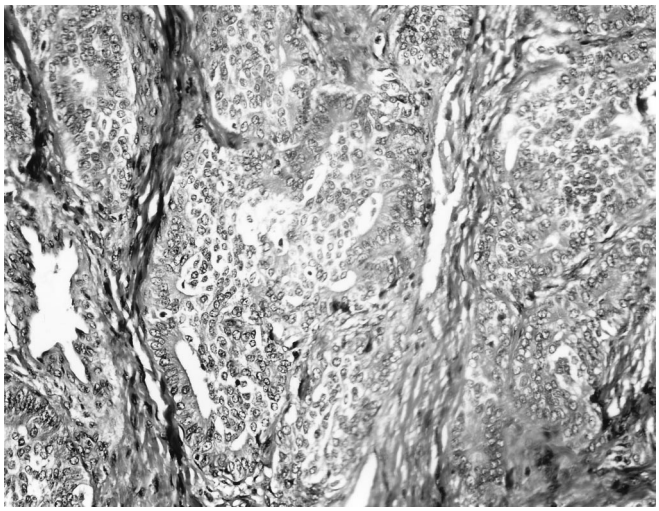


Fig. 5. Three cases showed foci resembling adamantinoma: peripheral columnar cells surrounding central areas with loose polygonal cells.

(Fig. 4). Cells lining papillary and glandular areas were commonly tall with prominent centrally placed nuclei. In cribriform areas, the epithelium was flattened and attenuated, often back to back in the septa between spaces. In the solid areas, there was a range of cytologic appearances; five tumors showed areas with a pattern reminiscent of hyalinizing trabecular tumors, and in three the outer layer of cells pallisaded around solid areas of tumor, producing a pattern similar to that of adamantinoma (Fig. 5). In general, the nuclei of these tumors were normochromic, lacking the pale, dusty chromatin or Orphan Annie appearance typical of papillary carcinoma. Intranuclear holes (cytoplasmic inclusions) and grooving of the nuclear membrane were present, but these changes were less prominent than in classic papillary carcinoma (Fig. 3). Five cases demonstrated psammoma bodies.

Treatment

Surgical treatment consisted of total thyroidectomy in five patients, near-total thyroidectomy in another five, and unilateral lobectomy in two. Five patients underwent postoperative adjuvant therapy with iodine-131 (^{131}I). Ten patients were placed on long-term levothyroxine (T_4) suppression.

Long-Term Results

The mean follow-up was 142 months (range 7 months to 30 years). No patient developed distant metastases. Regional recurrent disease occurred in two patients: One patient (21-year-old woman) had three recurrences, at 1.0, 2.0, and 2.5 years, respectively, all of which were treated with local resection. The second patient (36-year-old woman) had two recurrences at 6.0 months and 7.0 years following the initial operation. The first recurrence was treated with a laryngectomy, radical neck dissection, and external radiation therapy. The second recurrence presented as extensive local disease. This patient died 1 month later at age 36 of cardiac tamponade secondary to extensive mediastinal adenopathy.

The computed Kaplan-Meier estimates of survival for the observed sample of patients with FAP and thyroid cancer appears to be lower than the expected survival for an age- and sex-adjusted population (expected curve of whites from the west-north central area of the United States. The observed curve shows a 90% probability of survival 5 years from the time of thyroid cancer diagnosis and 77% at 20 years. This survival is also less than expected for sporadic papillary thyroid cancer patients, as defined by the MACIS prognostic scoring system [13]. Using this scoring system, all of our patients have a score less than 6 (mean 4.10, range 3.4–5.6), which places them in the low-risk category, with a 99% twenty-year cause-specific survival rate. The expected 20-year survival of 77% is lower than predicted and is compatible with the survival of the intermediate-risk category, which has expected 20-year survivals of 89% (score 6.0–6.99) and 56% (score 7.0–7.99).

Discussion

Is there, in fact, an increased incidence of thyroid carcinoma in patients with FAP? Papillary thyroid carcinoma is the most common thyroid cancer and accounts for about 80% of primary thyroid malignancies. Sporadic papillary thyroid cancer typically occurs in women (female/male ratio 3:1) in their fifth decade of life. The disease in these patients is typically solitary and unilateral. In the United States the prevalence of the disease is estimated, with age and sex adjustment, to be 4.6 per 100,000 population [14].

Accurate data regarding this question of increased prevalence is dependent on the accuracy of FAP registries and the extent of screening of patients in such registries for thyroid abnormalities. In addition, the referral bias of all registries must be assumed and understood. The uncertainties of any FAP registry are that: (1) not all patients with FAP end up in a registry; (2) perhaps only "complicated" FAP patients end up in a registry; and (3) certainly only a few FAP patients undergo thorough thyroid gland evaluation. One could therefore argue that the prevalence of thyroid carcinoma in FAP registrants could be either over- or underestimated. In the present study, the prevalence was 7 of 1320 FAP patients at the Mayo Clinic and 6 of 1434 (2 patients were excluded from our study due to lack of slides for review) at the Cleveland Clinic. These numbers translated into a prevalence of

399 per 100,000 (11/2754) FAP patients, respectively. A study from the Johns Hopkins FAP registry [8], interestingly, revealed a risk of 26.8 cases per 100,000 person-years with an increased relative risk of 7.6 (95%) (confidence limits 2.5–17.7). A classic earlier study [6] of patients in the FAP registry at St. Mark's and St. Mary's Hospitals in London found a staggering incidence of 4819 per 100,000 population in contrast to their estimated incidence of 30 per 100,000 in the general, non-FAP population. The authors concluded that "from these calculations a young female patient with adenomatous polyposis can be seen to have a 160 times greater than expected chance of developing a thyroid carcinoma before the age of 35." This study was corroborated by a Danish study [7], which revealed a 100-fold increase of observed versus expected cases of thyroid carcinoma in Danish patients with FAP. This study is particularly noteworthy because it represents data in a registry with virtually total coverage for a single country.

Because the data regarding the increased incidence of thyroid carcinoma seems nonrefutable, how can FAP patients best be screened? Perhaps more intriguing: if a young woman is found to have a multicentric, bilateral papillary carcinoma with the "unusual" histologic features described in our patients, should she be screened for FAP? The answer to the latter scenario should be in the affirmative (proctoscopy, colonoscopy, colonic contrast studies). In the former scenario, it seems prudent to include examination of the thyroid gland in the routine clinical assessment of the patient (particularly the young woman) with FAP. If there is any suspicion regarding a thyroid abnormality(ies) on physical examination, liberal use should be made of high-resolution ultrasonography of the neck with or without fine-needle aspiration biopsy.

There should be no controversy regarding treatment of the thyroid malignancy. In light of the high incidence of both multicentricity and bilaterality, total thyroidectomy with routine regional nodal sampling seems prudent. Particular care should be employed in this young patient population to preserve the parathyroid glands, thereby avoiding the need for cumbersome calcium supplementation. We advocate a liberal policy of immediate parathyroid transplantation when the parathyroid gland(s) cannot be preserved in situ. Life-long thyroid-stimulating hormone (TSH) suppression by thyroxine (T_4) administration is a sine quo non, as is the use of ^{131}I scanning and ablation in those patients with metastatic disease or those with tumors > 2.0 cm in diameter.

Is the thyroid malignancy that occurs in FAP patients simply a coincidental finding, or is it a disease due to a genetic aberration [perhaps the antigen-presenting cell (APC) gene on chromosome 5q21] as in FAP? FAP is known to be associated with neoplasia of various other tissues in addition to thyroid cancer [2, 3]. It seems that the germline mutation of the APC tumor-suppressor gene responsible for FAP [15] might also be involved in the pathogenesis of thyroid cancer. Studies have not demonstrated significant alterations in the mutation cluster region (MCR) of the APC gene in cases of sporadic thyroid cancer [16, 17], which suggests that alterations of the tumor-suppresser gene *alone* do not represent a frequent event in thyroid *tumorigenesis*. There has been no study to assess APC gene involvement in the distinctive variant of thyroid cancer that occurs in FAP patients, but we are currently studying this question. We know that this cancer is histologically different from the sporadic or classic type; [12] therefore it is reasonable to believe that as a different type of tumor it may show a different pattern of oncogene mutations. The finding that only a few FAP patients have thyroid tumors and that the tumors are commonly multiple suggests that other genes, acting in cooperation with the APC gene, are involved. The surprising frequency of female patients, compared to male patients, with thyroid tumors in association with FAP, which is caused by an autosomal gene, suggests that a sex hormone-responsive gene might be important. The presence in our one male patient of a papillary cancer that had usual histology probably represents a sporadic/spurious event.

Conclusions

This study confirms the observations of other investigators who have detailed the clinical and pathologic features of patients with FAP and thyroid carcinoma. In particular, our study emphasizes the unique histopathologic features of the thyroid malignancy in patients with FAP. The finding of such unique histopathology may in fact be distinctive enough to warrant screening for FAP, particularly if the patient is a young woman with a multicentric, bilateral thyroid carcinoma but no evidence of multiple endocrine neoplasia syndrome. The genetic mutation responsible for the thyroid carcinoma awaits elucidation. Surgical treatment of the thyroid carcinoma should follow the well established principles for the treatment of well-differentiated carcinoma, with total thyroidectomy being the treatment of choice in view of the high incidence of multicentricity.

The true prevalence of thyroid carcinoma in patients with FAP cannot be established until a large cohort of FAP patients is carefully screened prospectively by thyroid palpation and ultrasonography with liberal use of fine-needle aspiration. Our data support the notion that the prevalence of thyroid carcinoma in patients with FAP is markedly increased compared to that in non-FAP patients, and that careful evaluation of the thyroid gland is prudent in all FAP patients.

Résumé

Bien que rare, l'association entre un cancer de la thyroïde et la polypose adénomateuse familiale (syndrome de Gardner) est bien connue. On a suggéré que dans ces cas, les tumeurs de la thyroïde avaient des caractéristiques histologiques uniques et sont d'origine folliculaire. En raison de leur basse prévalence, cependant, le traitement et le pronostic à long terme de cette association ne sont pas bien connus. *Méthodes*. On a revu des dossiers de 12 patients (prévalence 399/100,000) observés entre 1949–1995. L'histologie a été revue indépendamment par deux anatomopathologistes. *Résultats*. Il s'agissait d'onze femmes (deux soeurs) et d'un homme, d'un âge moyen de 28 ans (extrêmes 15–61 ans). Huit patients (66%) avaient des tumeurs multicentriques et cinq (42%), une maladie bilatérale. Le diamètre moyen de la tumeur était de 1.8 cm (extrêmes 0.2–5). Deux patients avaient des métastases ganglionnaires régionales. Les douze cancers de la thyroïde dans cette série étaient des cancers papillaires. Le seul patient de sexe masculin avait une histologie «typique» avec une architecture papillaire et folliculaire à des dégrés variables alors que les onze patientes femmes avaient des tumeurs dont l'histologie était atypique, bien décrite par Harach. Cinq patients (41%) ont eu une thyroïdectomie totale, cinq, une thyroïdectomie subtotale, alors que deux ont eu une simple lobectomie. Le suivi moyen a été de 142 mois (extrêmes 7 mois–30 ans). On a observé

une récidive régionale chez deux patients dont l'un en est décédé. La survie à cinq et à 20 ans a été, respectivement, de 90% et de 77%. *Conclusions*. (1) Toutes les tumeurs dans cette étude étaient papillaires, mais l'histologie était atypique dans 91%. (2) L'âge moyen (28 ans) était plus jeune que celui des patients ayant une maladie sporadique; (3) La maladie multicentrique et bilatérale est fréquente. C'est pour cette raison qu'il faut envisager une thyroïdectomie totale; (4) Le pronostic à long-terme est excellent. (5) La découverte d'une histologie inhabituelle chez un patient jeune ayant un cancer papillaire de la thyroïde devrait évoquer la possibilité d'une association avec la PAF.

Resumen

La asociación del cáncer tiroideo con la poliposis adenomatosa familiar, aunque rara, es bien conocida. Se ha sugerido que estos tumores tiroideos poseen características histológicas especiales y que su origen puede ser folicular. En virtud de su rareza, tanto el tratamiento como el pronóstico a largo plazo resultan inciertos. Métodos: Se hizo la revisión retrospectiva de 12 de tales pacientes (prevalencia 399/100.000) vistos en el periodo 1949–1995. La histología fue revisada en forma separada a por dos patólogos. Resultados: El grupo incluyó 11 mujeres (dos hermanas) y 1 hombre, con edad promedio de 28 años (rango 15–61). Ocho pacientes (66%) presentaban tumores multicéntricos y cinco (42%) enfermedad bilateral. El diámetro promedio del tumor fue 1.8 cm (rango 0.2–5). Se encontraron metástasis ganglionares regionales en dos casos. La totalidad de los doce cánceres tiroideos en esta serie fue del tipo papilar. El único paciente masculino demostró histología "típica" con una arquitectura papilar y folicular variable, en tanto que las 11 pacientes femeninas presentaban tumores con una histología inusual, tal como la describe Harach. Cinco pacientes (4%) fueron tratados con tiroidectomía total, cinco con tiroidectomía casi total y dos con lobectomía solamente. El seguimiento medio fue de 142 meses (7 meses—30 años). Dos pacientes desarrollaron recurrencia tumoral regional, uno de los cuales murió como consecuencia de la enfermedad. Las tasas de supervivencia a cinco y a veinte años fueron 90% y 77%, respectivamente. Conclusiones: (1) Todos los tumores en esta serie fueron del tipo papilar, aunque se encontró una histología atípica en 91% de ellos. (2) La edad promedio de los pacientes (28 años) es menor que la de los pacientes con enfermedad esporádica. (3) Tanto la enfermedad multicéntrica como la enfermedad bilateral son comunes. Por lo tanto, la tiroidectomía total debe ser considerada con firmeza. (4) El pronóstico a largo plazo es excelente. (5) El hallazgo de una histología inusual en un paciente joven con carcinoma papilar de la glándula tiroides, debe crear la sospecha de poliposis adenomatosa familiar.

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Invited Commentary

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Perrier and her colleagues make an important contribution to our knowledge. Their findings in 12 patients with familial Adenomatous polyposis (FAP) and thyroid cancer reveal that: (1) 11 of the 12 patients with thyroid cancer and FAP were female, including two sisters; (2) most patients are young at diagnosis (mean 28 years, range 15–61 years); (3) a "typical" histologic pattern occurs in patients with these papillary thyroid cancers; (4) the cancers are frequently multifocal (66%) and bilateral (42%); and (5) these papillary thyroid cancers are somewhat more aggressive than sporadic papillary thyroid cancer.

The authors briefly review other studies regarding the frequency of thyroid cancer in FAP families and document that there is a 100- to 160-fold increase in frequency of thyroid cancer in these patients. Because one-third of the patients presented with thyroid cancer before being diagnosed with FAP, the authors emphasize that it is most important for pathologists and surgeons to be aware of the "typical" histologic pattern of these papillary thyroid cancers so the patients can be appropriately managed. Such patients should be screened for colonic disease. The disease is often multifocal (66%), bilateral (42%), and aggressive. Therefore they recommend total thyroidectomy as the treatment of choice and postoperative ^{131}I therapy for those with invasive or metastatic disease or primary tumors > 2 cm in diameter.

It would be interesting to know from reviewing all reports of patients with papillary thyroid cancer and FAP whether the typical histology is always present. Do men as well as women develop these thyroid cancers, and does survival differ from that of patients with sporadic papillary thyroid cancers? Does treatment with total or near-total thyroidectomy with postoperative ^{131}I ablative treatment and thyroid-stimulating hormone (TSH) suppression therapy improve survival?

Since the development of genetic testing for *ret* point mutations by a simple blood test for identifying patients with familial medullary thyroid cancer, there has been an increased interest in identifying the gene or genes responsible for familial nonmedullary thyroid cancer [1, 2]. Familial papillary and Hürthle cell cancer accounts for about 6% of all of these cancers [3–7]. Thyroid cancers of follicular cell origin are also more common in patients with Cowden's disease and perhaps more common in patients with multiple endocrine neoplasia type I (MEN-I) and familial hyperparathyroidism [8–10]. Thyroid cancers also occur more commonly in Japanese patients with Werner syndrome, which predisposes patients to premature aging [11]. Although Caucasians also may develop Werner syndrome, they apparently do not develop thyroid cancer.

Several recent studies, including those of Ozaki et al. [3], Grossman et al. [4], and Takami et al. [5] but not others [6] suggest that familial nonmedullary thyroid cancer without other conditions such as FAP or Cowden's disease is somewhat more aggressive than sporadic thyroid cancer. More of these patients have multifocal and bilateral disease and nodal involvement, and recurrence is also more common. Patients with FAP and thyroid cancer seem to be similar. Hopefully, the gene or genes responsible for familial nonmedullary thyroid cancer unassociated with FAP or Cowden syndrome will be identified soon, so those at risk can be diagnosed at an earlier stage. This point is especially important, as aspiration biopsy for cytologic examination is not accurate in these patients (M. Vriens et al., 1998, submitted). Also of interest is whether patients who are carriers of the gene for familial thyroid cancer are at greater risk than others for developing thyroid cancer after exposure to low-dose radiation [12, 13]. The importance of genetic predisposition in patients with thyroid cancer is probably underestimated, but there is now considerable interest in this field.

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