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CASE REPORT

Familial Adenomatous Polyposis (Gardner's Syndrome) and Thyroid Carcinoma

A Case Report and Review of the Literature

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KEY WORDS: familial adenomatous polyposis; Gardner's syndrome; thyroid carcinoma.

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by hundreds to thousands of adenomatous colonic polyps that first appear during childhood or adolescence. The manifestations of this disorder were extended beyond the colorectum in 1951 by Gardner (1), who described a family with intestinal polyposis and multiple soft tissue and bony tumors that were subsequently characterized as multiple osteomas, epidermoid cysts, and cutaneous or subcutaneous fibromas (2). The triad of FAP, osteomas, and soft tissue lesions, often referred to as Gardner's syndrome, is now recognized to include other extracolonic lesions, including retinal pigmentation (3–5), desmoid tumors (6, 7), gastric and upper intestinal adenomas (8) and carcinomas (9), pancreaticobiliary adenomas (10), hepatoblastomas (11), and dental abnormalities (12). Turcot et al (13) described a brother and sister with FAP who had malignant central nervous system tumors, an association sometimes referred to as Turcot's syndrome (14). Other lesions have been associated with FAP, but it is difficult to be certain whether they are coincidental occurrences or part of the genetic defect (15, 16).

In 1968 Camiel et al (17) reported two sisters with FAP who developed thyroid carcinoma and suggested that this was another manifestation of FAP. In 1987, Plail et al (18) reviewed 998 patients with FAP and found that thyroid carcinoma occurred with greater than expected frequency. Little has been written about the natural history of thyroid carcinoma associated with FAP, and authorities' recommendations differ regarding screening patients with FAP for thyroid disease. Some suggest screening for thyroid carcinoma by palpation (18), others recommend ultrasonography (19), and still others feel that screening FAP patients for thyroid carcinoma is not indicated (15) because it may cause "cancerphobia." We report a patient with FAP and papillary thyroid carcinoma and review the literature with special attention to features that might predict the behavior of thyroid carcinoma occurring with FAP.

An electronic literature search (Dialog Information Services Inc. Palo Alto, California) for articles in all languages was performed using the following descriptors: papillary thyroid carcinoma, thyroid neoplasms, familial polyposis syndrome, Gardner syndrome, or pigmentation disorders. In addition, the authors' reference files and references in several recent excellent reviews (15, 16) of FAP were carefully scrutinized. Only published papers of thyroid carcinoma in subjects with endoscopically or surgically documented FAP or members of FAP families with extracolonic manifestations of the syndrome were accepted for inclusion in this review.

CASE REPORT

A 24-year-old white woman, mother of two children, was referred to Madigan Army Medical Center because of a four-month history of bloody diarrhea unaccompanied

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by weight loss or other systemic symptoms. Her previous health had been good and she denied exposure to ionizing radiation. Her physical examination was normal except for multiple pigmented spots on both retinae, numerous soft subcutaneous tumors thought to be epidermoid cysts located mostly on her extremities, and a 3-cm palpable nodule in the right thyroid lobe without cervical adenopathy. Colonoscopy disclosed hundreds of polyps from the rectum to cecum. Esophagogastroduodenoscopy was normal and panorex view of the mandible showed no bony abnormalities. Total colectomy was done. The entire mucosal surface of the colon and rectum was studded with hundreds of polyps, which histologically were tubulovillous adenomas. A month following her colectomy a fine-needle thyroid aspiration biopsy yielded cytology consistent with papillary thyroid carcinoma. She underwent total thyroidectomy. Her right thyroid lobe contained a single 1.9 × 0.8 × 0.8-cm papillary thyroid carcinoma, which did not extend beyond the thyroid capsule. The remainder of the thyroid was normal. After appropriate preparation, a total body ^{131}I scan disclosed tracer uptake only in the thyroid bed. She was given 100 mCi of ^{131}I followed by levothyroxine at a dosage sufficient to suppress her serum TSH concentration. The patient was adopted and a complete family history was unavailable. Her biological mother, 45 years old, was healthy and had no gastrointestinal complaints. No information was available concerning the patient's father. Her 6-year-old son underwent sigmoidoscopy, which was normal, but an ophthalmologic consultant noted numerous pigmented lesions on both of his retinae. Her 16-month-old son is presently without evidence of disease.

DISCUSSION

Although FAP has an autosomal dominant mode of inheritance, more than 40% are isolated cases (15), which occur either by coincidence, with the patient being the only affected member in their generation, or may represent new mutations. Our patient's 6-year-old son had a normal rectal and sigmoid examination, but displayed retinal pigmentation and undoubtedly has FAP (5). Polyps due to FAP rarely develop before the age of 10 years and typically are first seen around 16 years of age (15). Patients ordinarily experience their first bowel symptoms (bleeding, diarrhea, mucus discharge) by age 30, and without colectomy 100% develop colorectal carcinoma in their mid-30s which results in death by age 40 (15). An occasional patient develops colorectal carcinoma under the age of 20 (16).

The multiple bilateral retinal pigmented lesions displayed by our patient's son are an important clue to the diagnosis of FAP. These lesions, which are due to congenital hypertrophy of the retinal pigment epithelium, when encountered in the normal population are isolated, small, unilateral lesions. In FAP they are often present at birth or soon thereafter and are a good marker of the syndrome (4–6). In a study of 134 members of 16 FAP kindreds, Traboulsi et al (4) found about 90% of those affected had pigmented retinal lesions, which were bilateral in 78% of the cases. The presence of bilateral or multiple lesions (more than four) or both had a specificity of 95% and a sensitivity of 78% for FAP. Heyen et al (5), in a study of 148 members of 53 FAP kindreds, found that more than four pigmented lesions distributed in both eyes is a marker for FAP, which was present in about 65% of the families studied.

The first documented association of thyroid carcinoma and FAP was in 1949 when Crail (20) reported a papillary carcinoma in a 24-year-old man with colorectal polyposis and medulloblastoma. Several other patients with thyroid carcinoma and FAP were documented in the 1960s (21–23), but the importance of this association was not fully appreciated until 1968 when Camiel et al (17) reported two sisters with FAP who developed papillary thyroid carcinoma, one at age 19 and the other at age 20. The authors suggested that the occurrence of FAP and thyroid carcinoma in siblings was more than serendipity. In a subsequent large study from London, Plail et al (18) estimated that a young female patient with FAP has a 160-fold greater than expected chance of developing a thyroid carcinoma before the age of 35. Bülow et al (33) estimated that the observed frequency of thyroid carcinoma among females in their nationwide Danish Polyposis Registry was 100-fold greater (95% confidence limits 12–361) than in the general population of their country.

To date, 37 cases, including the present patient, of thyroid carcinoma associated with FAP have been reported in the literature (Table 1) (17–21, 23–35). When the histologic diagnosis was mentioned (N = 26), papillary thyroid carcinoma accounted for 88.5% and follicular carcinoma for 11.5% of the neoplasms, which is the usual distribution of sporadic thyroid tumors reported from geographic regions with adequate iodine intake (36). When the patient's sex was mentioned (N = 35) in these reports, 94% were females and only 6% were males, giving a female-to-male ratio of 17:1, which is far in excess of the usual 3:1 ratio (37, 38). The average age at which FAP was recognized was 24.6 years (range 14–39) and at which thyroid carcinoma was diagnosed was 23.6 years (range 16–40), but only five patients were over age 30 and only one was over age 40 at the time their thyroid carcinoma was recognized. Sporadic papillary thyroid carci-

TABLE 1. DOCUMENTED CASES[A] OF THYROID CARCINOMA (TC) ASSOCIATED WITH FAMILIAL ADENOMATOUS POLYPOSIS (FAP)*

		Age[B]		Thyroid carcinoma			Therapy		Follow-up		
Author (year)	Sex	TC	FAP	Type	Number of Lesions	Size (cm)	Surgery	RAI	Years	Cause of death	Thyroid Ca recurrence
Crail (1949) (20)	M	24[C]	24	papillary	single[D]	2.5	(autopsy finding)		none	medullo blastoma	no
Raynham (1966) (21)	F	20	20	unknown	multiple[E]	NS[F]	total[G]	no	none	alive	—
Smith (1968) (23)	M	29	39	papillary	multiple	NS	total	no	10	alive	no
Camiel (1968) (17)	F	19	28	papillary	NS	NS	subtotal	no	9	alive	no
	F	20	29	papillary	multiple	NS	total	no	9	colon carcinoma	no
Smith (1973) (25)	F	19	26	papillary	multiple	NS	total	no	11	alive	no
Keshgegian (1978) (26)	F	21	14	papillary	multiple	NS	total	no	9	alive	no
Hamilton (1979) (27)	F	18	17	papillary	NS	NS	NS	no	2	alive	no
Lee (1981) (28)	F	23	32	papillary	multiple[H]	NS	subtotal	no	5	alive	yes[H]
Delamarre (1982) (29)	F	21	27	follicular	NS	4	total	yes	8	alive	no
Thompson (1983) (30)	F	24	22	papillary	multiple	NS	total	no	none	alive	—
Schneider (1983) (31)	F	37	33	papillary	single	NS	(autopsy finding)		none	sepsis	—
Plail (1987) (18)	F	22	21	papillary	multiple	2	total	no	2	colon carcinoma	no
	F	26	19	papillary	multiple	3	subtotal	no	7	alive	no
	F	34	31	papillary	single	3	subtotal	no	13	alive	no
	F	23	27	papillary	multiple	NS	total	no	19	alive	no
	F	20	20	unknown	multiple[E]	NS	excision	no	none	alive	no
	F	16	28	unknown	NS	NS	excision	external	12	alive	no
	F	34	17	unknown	NS[B]	NS	subtotal	no	11	alive	no
Piffer (1988) (19)	F	26	24	follicular	multiple	1	total	no	1	alive	no
	F	28[I]	NS	papillary	NS	NS	NS	NS	NS	thyroid carcinoma	—
	F	55[I]	NS	unknown	NS	NS	NS	NS	NS	thyroid carcinoma	—
Delamarre (1988) (32)	F	29	16[J]	papillary	multiple[K]	NS	total	yes	2	alive	—
	F	26	21[L]	papillary	multiple	NS	total	yes	3	colon carcinoma	no
Bülow (1988) (33)	F	19	17	papillary	single[M]	NS	subtotal	yes	2	alive	no
	F	NS	NS[N]	papillary	NS	NS	NS	NS	NS	alive	NS
	F	40	26	papillary	NS	NS	total	no	13	alive	no
van Erpecum (1988) (34)	F	34[O]	31	papillary	single[D]	3	total	no	2	alive	no
Herrera (1989) (35)	F	27	23	follicular	single[D]	NS	(autopsy finding)		—	sepsis	—
	F	NS	NS	papillary	single	NS	total	no	none	alive	—
Present case	F	24	24	papillary	single	2	total	yes	1	alive	no

*[A]Six other cases of FAP and thyroid carcinoma in the literature, two others reported by Smith (23) and four reported by Alm and Licznersci (24), were not included in this table because almost no clinical data, including the patient's ages, were given. Two other cases mentioned elsewhere in the literature as carcinomas were actually adenomas (14, 22). [B]Age in years at the time of diagnosis. [C]Present at age 14, diagnosed at age 24. [D]With capsular and/or vessel invasion. [E]Probably multiple, patient had a multinodular goiter with thyroid carcinoma. [F]NS = not stated. [G]Excision = uncertain extent of thyroid surgery; total = both lobes and isthmus, or "total" indicated by authors; subtotal = one lobe and isthmus, or "subtotal" indicated by authors. [H]Recurrence in opposite thyroid lobe. [I]Age at the time of death, not diagnosis. [J]Subsequently reported in Gastroenterol Clin Biol 13:229, 1989. [K]Bone metastases. [L]Previously reported in Gastroenterol Clin Biol 6:1016–1019, 1982. [M]Local nodal metastases. [N]3 years after thyroidectomy. [O]Present at age 31 and resected at age 34.

noma is usually diagnosed at least one to two decades later than this in most large series (36–38), while follicular carcinoma is ordinarily first identified at an even later age (39). The younger age of FAP patients could represent a selection bias since they often come under intense medical management early in their life when an incidental thyroid carcinoma may be discovered. However, in 30% of the patients, thyroid carcinoma was diagnosed 4–12 years before FAP (mean 8.3 ± 2.6 SD), while it was discovered 1–17 years after FAP (mean 5.3 ± 5.2) in 55%. In the others, the two diagnoses were made simultaneously. Table 2 summarizes the ages at the time of diagnosis in the various subgroups and shows that, regardless of the sequence of diagnoses, the patients are almost always quite young when thyroid cancer is diagnosed.

Multiple thyroid lesions were mentioned in 64% of the patients in which information concerning tumor number was provided. With sporadic tumors,

TABLE 2. AVERAGE AGE AT DIAGNOSIS

Sequence of diagnosis	*Thyroid carcinoma*	*FAP*
Thyroid carcinoma first	21.3	29.5
FAP first	27.8	22.2
Together	22.0	22.0
All cases	23.6	24.6

the frequency of multicentricity can be as high as 88% (40), but is only 20–30% when routine pathologic sections are done (36, 37). Only one patient (4.2%) with FAP had distant metastases of thyroid carcinoma. Local nodal metastases were mentioned in one other patient. Two deaths from thyroid carcinoma were reported; but only one was attributed to papillary carcinoma, resulting in an overall mortality rate of 4.2% after a follow-up that averaged 7.2 years in 21 patients. The papillary carcinoma death occurred in a 28-year-old woman about whom few details were reported (19).

Opinions vary about the proper approach to screening patients with FAP for thyroid carcinoma (15, 18, 19). In our view, the high frequency of clinically apparent thyroid carcinoma in patients with FAP warrants aggressive thyroid screening. Survival rates with FAP have been improved considerably in recent years with the advent of routine screening colonoscopy and early colectomy. The Danish FAP study reported that 10-year survival rates had increased from 13% in 1900–1949, to 53% in 1950–1969 and 70% in 1970–1982 (15). Accordingly, patients with FAP are living longer and can be expected to have more difficulty with extracolonic manifestations of FAP. Papillary thyroid carcinoma generally has an indolent clinical course with low mortality rates, but the disease becomes progressively more aggressive with advancing age, and patients begin experiencing increasingly higher mortality rates with each passing decade after age 40 (36–38). It would seem prudent to screen FAP patients carefully with both thyroid palpation and ultrasonography and to biopsy lesions that are over 1 cm in diameter (41, 42). Since multicentric thyroid carcinomas were found in 64% of patients with FAP, total or near-total thyroidectomy should be done for suspicious lesions, followed by thyrotropin suppression with levothyroxine. Large (>1.5 cm), multicentric lesions should be considered for radioactive iodine (^{131}I) therapy (36).

Since almost 30% of thyroid carcinoma cases have been diagnosed 4–12 years before polyposis, young patients presenting with thyroid carcinoma should be questioned regarding bowel function and a family history of gastrointestinal disease, and consideration should be given to periodic testing for fecal occult blood.

SUMMARY

The case history of a 24-year-old woman with Gardner's syndrome [familial adenomatous polyposis (FAP)] and papillary thyroid carcinoma is presented, representing the 37th report of this association. Although FAP is transmitted as an autosomal dominant trait with similar penetrance in both sexes, thyroid carcinoma has been found almost exclusively in women (94.3%). The majority have been papillary carcinomas (88.5%), which have become apparent during the third decade (average 23.6, range 16–40 years). Most (55.5%) thyroid carcinomas have been discovered 1–17 years after FAP was identified, although some have been found before (29.6%), or at the same time (14.8%) FAP was diagnosed. Multicentric papillary carcinomas have been reported in 64% (14 of 22) of FAP patients, a frequency at least twofold greater than usual. Although papillary carcinoma found before age 30 (as it was in most patients with FAP) typically has an excellent prognosis, one patient with FAP developed distant metastases from thyroid carcinoma and a 28-year-old woman's death was attributed to papillary carcinoma. The high frequency of multicentric papillary thyroid carcinoma in young patients with FAP and the potential for metastases and death due to thyroid carcinoma warrant aggressive diagnostic screening at regular intervals with neck palpation, ultrasonography, and if necessary, fine-needle aspiration biopsy. When thyroid carcinoma is found, total or near-total thyroidectomy should be considered because of the tumor's high likelihood of being multifocal. Since almost 30% of the thyroid carcinomas associated with FAP have been diagnosed 4–12 years before polyposis was identified, young patients presenting with thyroid carcinoma should be questioned regarding bowel function and a family history of gastrointestinal disease, and consideration should be given to periodic testing for fecal occult blood.

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