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Papillary thyroid cancer in two sisters

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Case reports on two sisters with histologically confirmed papillary thyroid cancer are presented. Gastroenterological examinations were normal in both patients, Gardner's syndrome excluded. It was concluded that family history, clinical presentation free of underlying cancer syndrome, and histopathologic examination are not adequate for reliable differentiation between occasional and familial forms, unless genetic markers are available.

Key words: thyroid neoplasms; Gardner's syndrome, thyroiditis, autoimmune

Introduction

In contrast to medullary thyroid carcinoma (MTC) which, in part, shows familial occurrence as a part of multiple endocrine neoplasia syndrome type 2 (MEN 2), the nonmedullary forms of thyroid cancer are not generally thought to present familial occurrence. However, evidence from literature[1-6] on thyroid cancer associated with familial adenomatous gastrointestinal polyposis (Gardner's syndrome) suggests possible inheritance. In a majority of familial cases, papillary cancer has been described, almost exclusively in young females, as being twice more often multicentric in origin, affecting both lobes of the thyroid gland, diagnosed before the age of 30, and with excellent outcome.[2-6]

In this case report, we present two sisters with papillary thyroid cancer. The aim of evaluation was to determine whether these cases could be considered a familial disease.

Case report 1

In 1982, P.A., a 42-year-old woman, presented at our Department for suspect hyperthyroidism. The patient's mother had died from leukemia. There were no other severe diseases or patients with gastrointestinal disease in the family.

The patient complained of palpitations, nervousness, inappetence, nausea, diarrhea and weight loss. She was not aware of thyroid gland enlargement. On physical examination, a solitary 1.5 x 1.5 cm palpable nodule was found in the left thyroid lobe. The right thyroid lobe was enlarged but free of any palpable nodules. Scintigraphy using Tc-99m and I-131 showed the palpable nodule to be a "cold" one. Ultrasonography of the thyroid was not performed. Serum thyroid hormone values were normal, thyroglobulin and thyroid microsomal autoantibody levels were negative. Fine-needle aspiration biopsy (FNAB) of the nodule was cytologically diagnosed as papillary carcinoma. The cytologic finding indicated surgical ablation of the left thyroid lobe. Histologic examination of the surgical specimen showed macroscopically a peripheral gray solid tissue, 1.8 cm in diameter, with an encapsulated nodule of 1.6 cm in diameter. Microscopically, tumorous tissue was found to be composed of papillae with thin fibrovascular core, covered with one layer of tumor cells with ground-glass nuclei. The nemerous follicles were covered with large cells with cytoplasmic pseudoinclusions. After one month, surgical ablation of the right lobe was performed. Hystology showed no malignant elements. There was no infiltration of the lymph nodes either.

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After total thyroidectomy, an ablative dose of iodine-131 of 1.85 Gbq (50 mCi) was administered. In 1984, total body imaging showed enhanced accumulation of iodine-131, located in the projection of the right thyroid lobe, which was considered a local recurrence. An ablative dose of 4.44 GBq (120 mCi) of iodine-131 was administered.

In 1987, her sister (Case 2) was examined at our Department. She had enlarged thyroid gland and a cytologic finding suspect of medullary thyroid carcinoma. In view of the possibility of familial medullary thyroid cancer also considered in the former patient, histologic findings of both surgical specimens were demanded again. However, papillary carcinoma was verified on reexamination. Serum calcitonin levels measured before and after stimulation with ethanol were normal.

Other close family members were also examined. In a third sister, a discretely enlarged thyroid gland, normal concentrations of triiodothyronine and thyroxine, and positive titres of microsomal autoantibodies were found. Iodine-131 scintigram showed a homogenous activity distribution, while FNAB pointed to chronic lymphocytic thyroiditis. Gastroenterological examination was also performed for possible association with Gardner's syndrome. Gastroscopic and colonoscopic findings were normal in all the three sisters.

Case report 2

Š.A., a sister 7 years younger than the latter patient, presented at our Department at the end of 1984, with enlarged thyroid gland. During the preceding four years, she had elevated blood pressure reaching 220/130 mmHg, irregularly treated with antihypertensives, accompanied by hot flushes. She often suffered from nausea, vomiting and diarrhea, regardless of the food taken. On physical examination, an enlarged left lobe and isthmus were found, with no markedly palpable nodules. Scintigraphy with Tc-99m and I-131 showed an inhomogeneous activity distribution in the silhouette of the enlarged gland. Ultrasonography of the thyroid was not performed. The FNAB cytologic finding was suspect of medullary carcinoma. Total thyroid hormone levels were normal, and thyroglobulin and thyroid microsomal autoantibody levels were increased. The basal serum calcitonin level was normal, whereas after stimulation with ethanol and pentagastrin it was twice above the baseline. Surgery was advised, but she refused operation. She did not present at the Department until 1986. At that time, an enlarged thyroid was found, with two separate palpable nodules in the left lobe and isthmus, sized 1.5 x 2.0 cm each, but not "cold" on scintigraphy,Repeated FNAB was suspect of medullary carcinoma again. Repeated measurements of serum calcitonin level before and after stimulation with pentagastrin and ethanol were normal. As medullary thyroid cancer was cytologically suspected, and considering the possibility of MEN 2 syndrome, further evaluation was undertaken. The urinary excretion rate of vanillylmandelic acid value measured in a 24-hour collection was normal. Computed tomography scanning of the abdomen was normal. Total thyroidectomy was performed in 1987. The histologic section showed two nodules, 1.5 x 2.0 x 1.0 cm and 3.0 x 3.0 x 3.0 cm in dimension. Histologically, the both were tumorous tissue of papillary structure, the papillae were covered with one layer of cylindrical epithelial cells with light and bullous nuclei. In the right lobe, numerous follicles of different size were found, covered with one layer of epithelial cells filled with dense eosinophilic colloid. A lymphocytic infiltration with numerous germinative centers was observed, and follicles in these areas were destroyed. After the surgery, an ablative dose of 3.7 GBq (100 mCi) of iodine-131 was administered.

Both sisters presented for clinical examination every 6 months, with annual chest x-rays and whole body iodine-131 scans. Until 1995, control examinations did not show any sign of propagation of the disease in either of them. Thyroglobulin levels measured annually were normal. Hypothyroidism was oversubstituted with 200 μg of L-thyroxin daily in order to completely suppress TSH secretion.

Discussion

The diagnosis of papillary thyroid cancer was undoubtedly confirmed histologically after thyroidectomy in both sisters. Due to familial occurrence of thyroid cancers, the patients were examined for hereditary MTC, which is the best known form of familial thyroid cancer. When MTC was excluded, the familial non-medullary form of the disease was established. Review of the literature suggested that there may be two groups of familial non-medullary thyroid cancer: one in which association of non-medullary thyroid cancer with inherited cancer syndrome (Gardner's syndrome and Cowden's disease)[2–7] could be documented, and another one in which familial papillary cancer is independent of the un-

derlying syndromes.[8-14] The incidence of papillary carcinoma in Gardner's syndrome is estimated to be 160-fold that in normal population.[6] The association of papillary carcinoma and possible hereditary cancer syndrome was not confirmed in our patients. As DNA analysis was not performed in our patients, it was difficult to conclude that our cases had a hereditary basis independent of the association with the underlying syndrome.

At the time of making the diagnosis, both sisters were middle-aged, while in other studies of familial occurrence of papillary carcinoma the patients almost exclusively were younger females. The malignant disease did not affect the contralateral thyroid lobes in our patients, although other authors found dissemination into both lobi of the gland in cases of familial papillary carcinoma.[2-5, 7] There were no distant metastases or increased thyroglobulin levels during the postoperative follow-up, suggesting a good outcome, which is consistent with other reports.[2, 3, 5, 7] In one sister, chronic lymphocytic thyroiditis was found. It was also diagnosed in the third sister. Lote and al. examined the thyroid surrounding tissue in their patients with familial papillary thyroid cancer, looking for possible focal thyroiditis with no confirming results.[12] On the other hand, others report on a significantly increased incidence of primary hypothiroidism in families with a familial form of papillary thyroid cancer, as a consequence of chronic lymphocyte thyroiditis.[9, 15, 16]

We accept suggestions of most authors that examinations should also include other close relatives when two or more members of the family have papillary carcinoma.[3, 4, 9] Families with papillary thyroid cancer should also be gastroenterologically examined in order to find possible associated polyposis, and *vice versa*, familial gastrointestinal polyposis should be examined for possible associated papillary thyroid cancer.

We conclude that family history, clinical presentation without underlying syndrome, and histopathologic examination are not adequate for reliable differentiation between occasional and familial forms, unless genetic markers are available.

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