

Familial Papillary Thyroid Cancer: A Case Report

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Abstract

Familial occurrence of medullary thyroid cancer is well known in families as an isolated malignancy or in association with multiple endocrine neoplasia syndrome type II. Conversely, papillary thyroid cancer almost always presents sporadically except for reports of familial clustering in individuals with radiation exposure, inherited syndromes of colonic polyposis or multiple hamartomas, and rarely in monozygotic twins. We report a case of papillary thyroid cancer diagnosed incidentally in a 53-year-old woman who underwent surgery for excision of an adenomatous nodule. It was noted that her mother suffered from a similar thyroid malignancy some 33 years ago, and several of her maternal relatives had either Graves' disease or hypothyroidism. The possible existence of this distinct familial entity and its likely genetic basis is discussed.

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Introduction

Robinson and Orr¹ first described familial occurrence of papillary thyroid cancer in a pair of identical female twins, both presenting with thyroid malignancies at the age of 24 years. Subsequent familial clustering of papillary thyroid cancers was noted in families with history of Gardner's syndrome (familial adenomatous polyposis),^{2,3} Cowden's syndrome (multiple hamartomas),⁴ congenital neurosensory deafness,⁵ and radiation exposure to the head or neck.^{6,7} The pathogenesis of these familial thyroid neoplasia are quite evidently linked to both genetic and environmental factors. Familial occurrence of papillary thyroid cancer independent of these associations, however, was first described by Lacour and colleagues⁸ in 1973 in the French literature, which involved a father and the daughter. The first report of familial nonmedullary thyroid cancer in the English literature was by Nemec and colleagues⁹ in 1975, involving a son and the mother. The latter suffered from follicular thyroid cancer and succumbed to widespread metastases. Since these early reports, there have been an increasing number of case reports on nonmedullary thyroid cancers occurring in families, with the majority of the papillary type.¹⁰⁻¹⁶ This supports the existence of a distinct familial subset in patients with papillary thyroid cancer. We report a kindred with the proband and her mother diagnosed with papillary thyroid cancer, and a

prevalent family history of thyroid diseases apart from thyroid cancer.

Case Report

A 53-year-old female was found to have a solitary right thyroid nodule two years ago. However, diagnostic evaluation was delayed due to various circumstances. During this interval, she noticed progressive enlargement of the nodule but was otherwise fully asymptomatic. She was referred for evaluation.

The patient had no complaints of hoarseness, dysphagia, weight loss, or symptoms of thyroid dysfunction. She had no history of thyroid disease, iodine or kelp ingestion, or radiation exposure to the head or neck. Family history was pertinent for papillary thyroid carcinoma in her mother, who had subtotal thyroidectomy for a suspicious thyroid nodule at age 43, some 33 years ago. This proved to be a solitary 1.25 cm intrathyroidal focus of papillary neoplasm with no cervical nodal or distant metastases. She has remained well since surgery. The family history was also remarkable for a high prevalence of other thyroid diseases, including the presence of Graves' disease, Hashimoto's thyroiditis, hypothyroidism, and goitre (Fig. 1).

On examination, the patient had a solitary 3 cm right thyroid nodule, which was soft and fully mobile on deglutition. The rest of the gland felt normal and there

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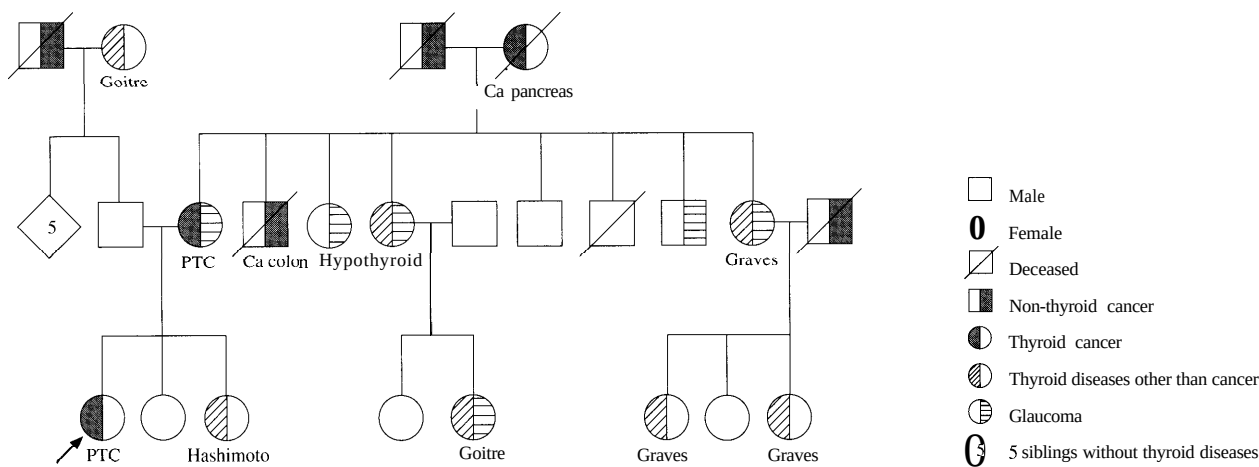
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Ca: Cancer; PTC: Papillary thyroid cancer; Hashimoto: Hashimoto's disease; Graves: Graves' disease

Fig. 1. Family tree with proband marked by arrow.

was no palpable cervical lymphadenopathy. Laboratory investigations showed normal levels of serum free thyroxine, thyroid stimulating hormone (TSH), and calcitonin; and she had negative anti-thyroid peroxidase antibody. Her chest radiograph was normal.

A fine needle aspiration cytology of the thyroid nodule showed no abnormal follicular cells but a few psammoma bodies were noted, thus raising suspicion for papillary thyroid cancer. A repeat procedure produced an insufficient yield. Subsequently, the patient underwent right thyroid lobectomy, and intraoperative frozen section examination of the nodule was consistent with a follicular neoplasm. This was confirmed by proper histologic examination to be a benign follicular adenoma. However, two microscopic foci of papillary thyroid cancer were found outside the nodule, the larger focus being 3 mm (Figs. 2a & 2b). She had completion total thyroidectomy, which also revealed another 1 mm focus of papillary thyroid cancer in the contralateral lobe. The cervical lymph node specimens were negative.

She remained well postoperatively and is scheduled for radioiodine ablative therapy of the thyroid bed in addition to thyroxine suppression therapy.

Discussion

Lynch and colleagues¹⁸ proposed the paradigm for familial neoplasia, which is characterized by an early age of onset, vertical transmission in consecutive generations, a smaller size of primary tumours, and a preponderance of multicentric and recurrent tumours. This paradigm exemplifies individuals with familial medullary thyroid cancer, which is caused by dominantly inherited activating mutations in the ret proto-oncogene.¹⁸ Conversely, familial papillary thyroid cancer most likely assumes polygenic inheritance and therefore affected individuals may not fit this paradigm well. The age of

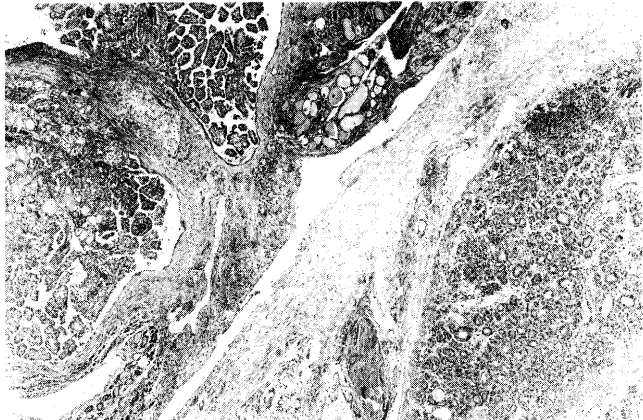


Fig. 2a. Photomicrograph demonstrating a well-encapsulated non-invasive microfollicular adenoma in the bottom-right portion, whereas the left portion of the field shows two nodules of well-differentiated papillary carcinoma. (x10, H & E)

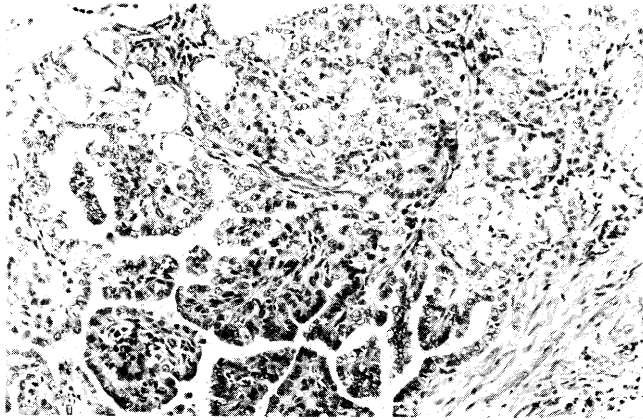


Fig. 2b. The lower portion of the field shows classic papillary carcinoma whereas the upper portion shows the follicular variant of papillary carcinoma. (x20, H & E)

onset in both the proband and her mother was not early compared to sporadic cases, although their primary tumours were small and multicentricity was noted in the proband. There was also no evidence of recurrence in the

mother after a follow-up period of more than 30 years. More clinical data from affected kindreds must be accrued before we could ascertain the paradigm for familial papillary thyroid cancer.

Two classes of genes are implicated in human tumorigenesis: i) oncogenes, the activation of which leads to growth stimulation and neoplastic proliferation, and ii) tumour suppressor genes, the loss of function as a result of deletion or alteration of which leads to tumorigenesis. Several oncogenes have been implicated in thyroid carcinogenesis. Activating mutations in GTPase *ras* oncogenes are thought to be an early event in tumorigenesis, as these have been detected in equal prevalence in both benign and malignant thyroid neoplasia.^{19,20} Gene rearrangements in receptor tyrosine kinase *ret* or *trk* proto-oncogenes, leading to upregulation of the tyrosine protein kinase activity, are likely to be specifically involved in the pathogenesis of papillary thyroid cancer.^{21,22} Rearrangements in *ret* proto-oncogene have been recently found in 15% to 20% of papillary thyroid carcinomas, although its association with familial occurrence has not been proven.²² Conversely, alteration or deletion of the p53 tumour suppressor gene is associated with undifferentiated anaplastic thyroid cancer. This is hypothesized to arise from well-differentiated forms via a multi-step process with loss of heterozygosity followed by deletion or mutation in the remaining p53 gene.²³ Familial papillary thyroid cancer is thus likely to have a heterogeneous and polygenic aetiology involving one or several of these implicated oncogenes.

The increasing number of reports over the past two decades on the familial occurrence of papillary thyroid cancer independent of genetic syndromes or radiation exposure supports the existence of a distinct familial subset in affected kindreds.⁸⁻¹⁶ In the first author's review of reported case series on familial nonmedullary thyroid cancers involving 178 affected individuals from 87 kindreds, up to 16% of the kindreds were found to have two or more affected first degree relatives.²⁴ Houlston and Stratton²⁵ estimated that a family with three affected members with papillary thyroid cancer would be expected to occur by chance less than once in every 100 years, thus dispelling the notion of fortuitous association.

It is noteworthy that an increased incidence of other malignancies, particularly cancers of the colon, stomach, kidney, breast and integumentary system, have been reported in kindreds with familial papillary thyroid cancer.^{10-12,15} Indeed, four of the relatives in our kindred succumbed to non-thyroid malignancies, two of whom had gastrointestinal tumours. In an Icelandic study on papillary thyroid cancer, Hrafnkelsson et al¹³ also found a significant excess of another primary malignancy among the female patients. The excess was largely due to breast, kidney and endometrial cancer. These associa-

tions may be caused by inheritance of common tumorigenic genes. The peculiar association of thyroid cancer and gastrointestinal neoplasia, including familial adenomatous polyposis, deserved molecular biological studies to elucidate common susceptibility genes. Current studies, however, fail to demonstrate somatic mutation of adenomatous polyposis coli (APC) tumour suppressor gene in subjects with sporadic papillary thyroid cancer, although no studies have been reported in familial cases.^{26,27} The continual surveillance for the presence of thyroid and non-thyroid malignancies in kindreds with familial thyroid cancer is therefore appropriate.

A high prevalence of other thyroid diseases has been observed in patients with thyroid cancer and their kindreds.²⁸ Stoffer et al¹¹ found benign thyroid disease in 7 of 20 immediate relatives of nine patients with papillary thyroid cancer diagnosed at age 20 or younger. This association may be even stronger in kindreds with familial thyroid cancers, as illustrated by our case. Grossman et al¹⁵ found thyroid disease other than cancer in 36% of the families with familial nonmedullary thyroid cancer, including follicular adenoma, hyperthyroidism, hypothyroidism, and goitre. An interesting feature in our kindred was the exclusive affection of females in either neoplastic or non-neoplastic thyroid diseases. The significance of a high frequency of angle-closure glaucoma noted in this kindred, especially among those individuals with thyroid disease, remained unknown.

The clinical course of the familial subset is reported to be more aggressive by several authors, as these tumours often have proclivity for multifocality or extrathyroidal invasion.^{9,12,15} In a review of 14 patients with familial nonmedullary thyroid cancers, Grossman et al¹⁵ found multifocal neoplasia in 13 cases (93%) and local invasion in 6 cases (43%). However, papillary thyroid cancer is well known for its multicentricity and figures as high as 65% is reported in a large series whereby total thyroidectomy specimens were available for careful pathologic examination.²⁹ Grossman et al¹⁵ reported tumour recurrences in 50% of cases during follow-up despite performing total or completion total thyroidectomy in all their patients. However, there are no reports to date of increased mortality from papillary thyroid cancer in the familial subset. Ozaki et al¹² reported 3 deaths in their series of 23 patients with familial nonmedullary thyroid cancer, but this included 2 patients with anaplastic cancer and one with unknown histology. Tumour dedifferentiation into the aggressive anaplastic variant may occur in about 1 % of differentiated thyroid cancers.³⁰ There is no data as yet to ascertain whether tumour dedifferentiation happens more frequently in the familial subset.

It is thus evident that with the current limited data, clinical and prognostic differences between the sporadic

and familial subsets, if any, are lacking. Nevertheless, the serendipitous discovery in our patient of multiple foci of papillary thyroid cancer outside the benign adenomatous nodule, underscores the importance of careful evaluation of thyroid abnormalities in individuals with family history of thyroid malignancies and/or other thyroid diseases. Some authors advocate up-front surgery if a solitary thyroid nodule is found in such an individual, however it has yet to be ascertained whether this aggressive approach will result in real benefit.¹⁵ Notwithstanding that we elected on empirical grounds to treat our patient more aggressively, she, like her mother, is likely to have an excellent course.

In conclusion, we report a kindred with familial predisposition to papillary thyroid cancer and other thyroid diseases. Familial occurrence of papillary thyroid cancer is extremely rare and it probably assumes polygenic inheritance. Apart from family screening and early treatment of affected individuals, the management philosophy for this rare familial subset remains empiric until sufficient data on its clinical course and prognostic outcome have been accrued.

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