

Papillary thyroid cancer: sporadic or inherited?

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Abstract

Background: Papillary thyroid cancer (PTC) is one of the most common thyroid malignancies, with an increase in incidence rates over the past few decades. Although the exact cause of thyroid cancer in most patients is still unclear, the possibility of genetic predisposition to PTC cannot be overlooked. Here, we report a case study of PTC, in which the family was extensively affected, with each family member diagnosed with either benign or malignant thyroid neoplasms, or functional thyroid disorder.

Method: A 57-year-old white female with a past medical history of hypothyroidism, and a significant family history of multiple thyroid cancers, was found to have new onset thyroid nodules during a routine screening ultrasound. Fine needle aspiration revealed suspicious papillary carcinoma (follicular variant). The patient underwent total thyroidectomy.

Results: The histology report revealed total colloid nodules in the right lobe with focal calcification, lymphocytic thyroiditis, and two foci of papillary microcarcinoma. The patient subsequently underwent radioactive iodine ablation therapy, along with pilocarpine and thyrogen injection.

Conclusion: This case study illustrates the need for awareness of the possibility of genetic predisposition to, as well as female preponderance of, familial PTC.

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Introduction

Papillary thyroid cancer (PTC) is a type of thyroid carcinoma with follicular cell origin, and is the most common and well-differentiated thyroid cancer. It accounts for > 85% of all thyroid lesions reported,^{1,2} with good prognosis and low mortality rate.^{2,3} The Surveillance, Epidemiology, and End Results database shows a 2.4-fold increase in the incidence of thyroid cancers over the last two decades.^{4,5} PTC is usually sporadic. At least five per cent of cases have a familial association, based on family studies and pathological examinations,⁶ and 3.5-6.2% of PTC patients have one, or more, first-degree relatives with thyroid carcinoma.¹ The familial forms of PTC are relatively rare. They include a heterogeneous group of diseases that incorporate both syndrome-associated tumors and non-syndromic tumors.^{7,8} Here, we report a case study in which several family members either had benign or malignant thyroid neoplasms, or thyroid disorders.

Clinical presentation and intervention

A 57-year-old white female with a past medical history of hypothyroidism (diagnosed at the age of 22), and on thyroxine replacement, was found to have thyroid

nodules during a routine screening ultrasound. The patient was advised to undergo a thyroid ultrasound screening due to a significant family history of multiple thyroid cancers (see Table 1). The patient had no history of change in weight, loss of appetite, heat or cold intolerance, alopecia, menstrual disturbance, or mood changes, nor any history of radiation exposure. Her past medical history was significant for migraines, oesophageal reflux, osteopenia, and hyperlipidemia. She is the second of 10 children. She has an extensive family history of thyroid disease, spanning three generations (see Table 1 and Figure 1). The patient's daughter had Hirschsprung's disease and arrhythmia, and died at the age of 14 from cardiac arrest. Her son has pervasive developmental disorder and Tourette's syndrome. The social history includes a remote history of smoking, but no alcohol or drugs.

Clinical examination revealed a euthyroid female, moderately built and nourished, with no ocular signs. The thyroid gland was not enlarged, and there was no cervical lymphadenopathy. The rest of the clinical examination was unremarkable. Laboratory data showed a total triiodothyronine 3 (T3) of 1.4322 nmol/l (0.9-2.8 nmol/l), free T4 of 11.583 pmol/l (8.5-

Table 1: Patient's family's history of thyroid disease

| Relationship to the patient | Disease conditions |
|---------------------------------------|---|
| Maternal grandmother | Hypothyroidism |
| Maternal grandfather | Prostate cancer |
| Mother | Hypothyroidism |
| Aunt | Ovarian cancer |
| Elder brother | Pulmonary embolus, unclear aetiology |
| The patient | Papillary thyroid cancer |
| Younger sister 1 | Hypothyroidism |
| Younger sister 2 | Thyroid nodule |
| Younger sister 3 | Papillary thyroid cancer at age 53, thyroidectomy, radioactive iodine |
| Younger brother 1 | Papillary thyroid cancer |
| Younger brother 2 | Thyroid nodule |
| Younger sister 4 | Graves' disease at age 30, papillary thyroid cancer at age 36 |
| Younger sister 5 | Thyroid nodule |
| Younger sister 6 | Papillary thyroid cancer |
| Niece 1: daughter of younger sister 1 | Hypothyroidism |
| Niece 2: daughter of younger sister 1 | Hypothyroidism |

15.5 pmol/l), thyroid stimulating hormone (TSH) of 1.66 mIU/l (0.5-4.70 mIU/l), antithyroid peroxidase antibody of 29 (< 60 lu/ml), creatine kinase of 190 U/L (26-174), and erythrocyte sedimentation rate of 19 mm/hour (0-20). Other laboratory data, including complete blood count and chemistry, were normal. Fine needle aspiration revealed suspicious papillary carcinoma (follicular variant). She underwent total thyroidectomy and the histopathology report showed colloid nodules in the right lobe with focal calcification, lymphocytic thyroiditis, and two foci of papillary microcarcinoma. The patient underwent radioactive iodine ablation therapy, pilocarpine and thyrogen injection, and a total body thyroid scan, after five to seven days. Testing for the phosphatase and tensin homolog mutation was negative. Currently, she is back on treatment with thyroxine, and a normal TSH level is being maintained. Regular follow-ups show no evidence of recurrence.

Discussion

The well-differentiated thyroid cancers, which include PTC and follicular thyroid cancer, comprise around 95% of total thyroid neoplasms. Even though the majority of PTC cases are sporadic, five per cent of PTC cases

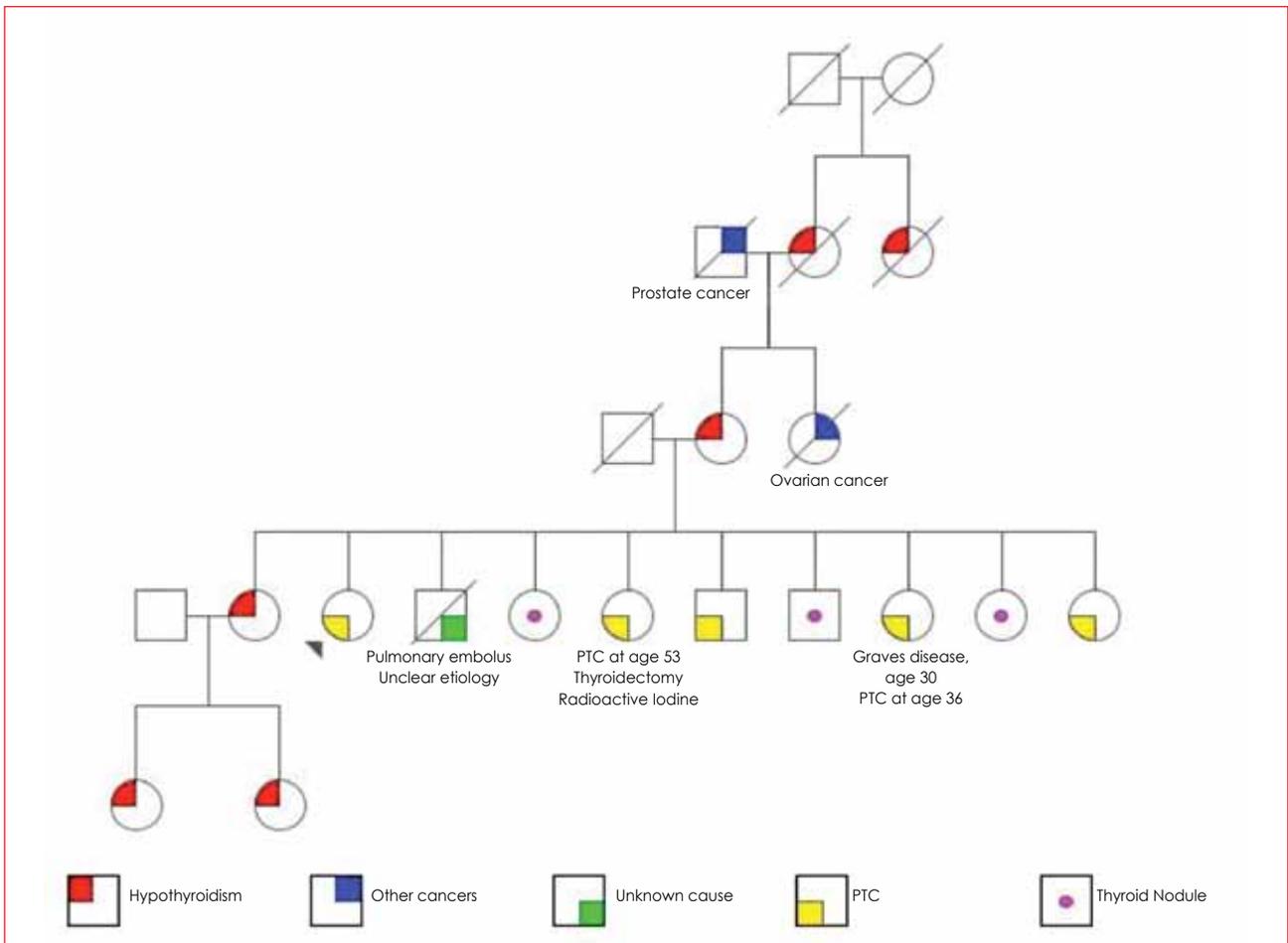


Figure 1: Pedigree chart of the patient's family. The patient is indicated by an arrow

have a familial association.⁹ Familial syndromes are characterised by the existence of three, or more, first-degree relatives with PTC, either with, or without, any other familial syndromes.⁹ Until recently, most of the research articles on familial PTC presented descriptions of individual family pedigrees, which has led to deliberations on whether the familial association is due to genetic predisposition, an environmental triggering event, or a mere chance occurrence.¹⁰ The case for familial PTC is slowly emerging from results of epidemiologic investigations, large genograms of PTC cases, and genetic research.⁸

According to a recent study, the familial risk ratio for individuals with a family history of PTC ranges from 8.6- to 10.3-fold of increased risk of developing a thyroid tumor, suggesting an inherited genetic influence on development of the disease.¹¹ This risk seems to be very obvious in our case, as it reveals a large kindred, in which multiple members of the family have either thyroid cancers, or thyroid disorders.

Familial nonmedullary thyroid carcinoma (FNMTC) may be classified as either syndromic or familial syndromes with a preponderance of nonthyroid tumors, or nonsyndromic or familial syndromes with a predominance of nonmedullary thyroid carcinoma.⁷⁻¹⁰ Our patient belongs to the second group, the nonsyndromic tumors, where the predominant neoplasm is nonmedullary thyroid carcinoma, although other neoplasms can occur in increased frequency in this group. The complete classification of FNMTC is shown in Table II.

Table II: Classification of familial nonmedullary thyroid carcinoma⁹

| Syndromic or familial syndrome with a preponderance of nonthyroidal tumors | Nonsyndromic or familial syndrome with a predominance of nonmedullary thyroid cancers |
|--|---|
| Familial adenomatous polyposis syndrome and Gardner's syndrome | Familial papillary thyroid carcinoma |
| PTEN ^a -hamartoma tumor syndrome | Familial papillary thyroid carcinoma, associated with renal papillary neoplasia |
| Peutz-Jegher's syndrome | Familial nonmedullary thyroid carcinoma type 1 |
| Carney's complex | Familial multinodular goiter |
| Werner's syndrome | |

a = phosphatase and tensin homolog

The relationship between a family history of thyroid cancer in first-degree relatives, and the risk of sporadic PTC, has been reported in a recent study by Xu et al.¹² This risk is still greater if the subjects have a family history

of thyroid cancer in siblings.¹² According to the findings of this study, the familial risk ratio of sporadic PTC was 4.6-fold higher in subjects with a first-degree family history of thyroid cancer, compared to subjects without that.¹² This indicates that a family history of thyroid cancer in first-degree relatives is associated with a significant increase in sporadic PTC risk.¹² However, as there might be some genetic association that is yet to be discovered, the association between an increased risk of sporadic PTC occurrence, and a family history of thyroid cancer in first-degree relatives, is debatable.

Individuals from our patient's family had coexisting thyroid disorders, either as thyroid nodules that were being monitored or as hypothyroidism. This illustrates the existence of a pattern of inheritance of familial PTC. It would be very interesting to know whether the patient and her family share a common gene, which could be responsible for a large number of thyroid disorders in a single family. Although a genetic analysis of this family was not undertaken (a PTEN mutation analysis was conducted, which was negative), it could be argued that PTC in this family is not an incidental finding.

The increasing incidence of PTC emphasises that there is a need for awareness of this syndrome. In susceptible cases, family screening may be warranted.

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