

Familial Thyroid Carcinoma

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We report a case of a 46 years old female who underwent total thyroidectomy in 1975 for papillary thyroid cancer. In 1985 she developed lymph nodes and lung metastasis for which she received radiotherapy.

In 1995 her mother was attending the Medical Clinic for bronchial asthma and noted to have a neck swelling which was associated with hoarseness of voice and difficulty in swallowing. A clinical examination followed by investigations proved that she was suffering from papillary carcinoma of the thyroid. Although familial thyroid carcinoma has been increasingly reported in the literature, we believe that these are the first two cases of familial thyroid carcinoma reported in Bahrain.

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Carcinoma of the thyroid is the most common endocrine cancer. Papillary thyroid cancer (PTC) is usually sporadic and evidence for a familial association of PTC (fPTC) (about 5% of cases) is based on family studies, epidemiological evaluations and pathology examinations¹.

Characteristics of fPTC include an association with benign nodular thyroid disease and autosomal dominant inheritance with age-dependant partial penetrance¹⁻⁴. There may be multiple susceptibility genes and/or modifying genes^{1,4-6}.

Recently, epidemiological studies reported an increased incidence of premenopausal breast cancer in women with PTC⁷, suggesting a common genetic predisposition to both disorders in some subjects.

Another study proved the genetic linkage between fPTC, nodular thyroid disease and papillary renal neoplasia (PRN)⁸.

Investigations of familial tumor syndromes often led to the identification of cancer susceptibility genes. These genes and their mutations provide not only critical insight into mechanisms of tumorigenesis, but also an opportunity for early diagnosis and therapy⁹.

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CASE 1

Forty six year old Bahraini female presented in 1975 with history of generalized body-aches, choking sensation, difficulty in swallowing, loss of appetite and neck swelling of two months duration. There was no history of change in weight, cold or heat intolerance, menstrual disturbance or mood changes. There was no past history of radiation exposure.

Clinical examination revealed an euthyroid female weighing 76 kg, with no ocular signs. Thyroid swelling was noticed mainly on the right lobe (grade II) which was hard in consistency, irregular and attached to the underlying structures. Cervical lymph nodes were enlarged on both sides, hard, 1cm x 1 cm in size and were discrete.

Fine needle aspiration cytology (FNAC) showed a papillary carcinoma of the thyroid gland. She underwent a total thyroidectomy. Operative finding was of a hard mass in the right thyroid lobe infiltrating the trachea which was sent for histopathology. It showed the tumor infiltrating the capsule, underlying muscles, vascular and lymphatic vessels. Left lobe showed normal histology.

In 1985, I-131 whole body scan was done which showed cervical lymph node and lung metastasis. Serum thyroglobulin was not measured.

A diagnosis of papillary carcinoma, follicular variant was made histologically for which she received a full course of radiotherapy.

She continued to suffer from breathlessness on exertion. Pulmonary function test showed "Restrictive lung disease" with low transfer factor, a diagnosis of "post radiation pulmonary fibrosis" was made. All the subsequent investigations which were carried out did not reveal distant metastases. Bilateral mammogram were normal.

In 1995 she was diagnosed as having Diabetes Mellitus and was treated with oral hypoglycaemic medication.

Currently she is on Thyroxin, where her TSH is maintained between 0.25-2.0 uIU/ml and oral hypoglycaemic agents. Regular follow ups shows no evidence of recurrence.

CASE 2

Sixty five years old Bahraini lady (Mother of our first patient), known to have Ischaemic heart disease and bronchial asthma with no past history of irradiation exposure. During her regular follow up in Medical Out-patients Clinic, she gave a history of hoarseness of voice of one year duration.

On examination she was clinically euthyroid, weighing 80kgs, with an enlarged thyroid, the left lobe more than the right one, hard in consistency. Lymph nodes were not enlarged.

FNAC showed papillary thyroid carcinoma. She underwent a near total thyroidectomy in June 1995. Left lobe thyroid mass and a small part of the right lobe was sent for histology. The diagnosis of papillary thyroid carcinoma with lymphatic vascular invasion was confirmed.

A whole body I-131 scan done in September 1995, revealed no evidence of abnormal tracer uptake in the lungs, gut or bony structures. Serum thyroglobulin was not measured before radiotherapy. As soon as the patient recovered she was started on L-Thyroxin replacement therapy.

DISCUSSION

Thyroid cancer is not a common disease, the incidence ranges between 1.5-10 per 10⁵ persons¹⁰. In most countries, papillary carcinoma is the most common histological type, comprising of about 40-70% of all thyroid carcinomas¹⁰⁻¹¹ and having the most favorable prognosis. Indeed, papillary carcinomas are unusually indolent and carry a low mortality rate (1-10%). Certain forms such as the tall cell and the insular variants are more aggressive but they are uncommon.

Women are more affected than men. Patient's age at the time of diagnosis is an independent risk factor. Prognosis depends on the extent of the disease within and outside the capsule.

Patients with a primary papillary thyroid carcinoma less than 1 cm in diameter have favourable prognosis. However, when the small primary lesion is accompanied by large regional metastases, the prognosis is not that favourable. Vickery et al found in 94 patients with primary tumor size of 1.5 to <3 cm, three recurrences (at rate of 2.4% for 10 years), one of whom had pulmonary metastases and died¹². Two of 45 patients (tumors size 3 to < 5 cm) developed pulmonary metastases 10-20 years after surgery.

The first patient had regional and distant metastases which were treated with surgical excision and radiotherapy, the patient is alive and in good health.

Familial occurrence of thyroid cancer is well established in medullary carcinoma, which occurs in multiple endocrine neoplasia (MEN) types 2A and 2B and in a familial form without associated neoplasia of other tissues.

Familial occurrence of non medullary carcinoma of the thyroid was first described by Smith^{13,14} as part of the familial adenomatous polyposis (FAP) syndrome. Later it was described as part of Gardner's syndrome¹⁵, a variant of FAP and it also occurs in Cowden's disease. Robinson and Orr¹⁶ in 1955 described twins with Familial Non-Medullary Thyroid Carcinoma (FNMTTC) not associated with FAP, 14 subsequent reports in the English literature of FNMTTC from another 52 families. The mean age of the patients was 38 years, and the male to female ratio of all affected individuals was 1:2.3.

The prevalence of FNMTTC among all cases of non familial thyroid cancer ranged from 3.5-6.2%.

In a large retrospective population-based study found a 5.8% prevalence of FNMTC among all Thyroid Carcinomas¹⁷.

The preponderance of women in FNMTC literature is consistent with an approximate sex ratio of 1:2 or sporadic Non Medullary Thyroid Carcinoma (NMTC) noted in large series.

In the family we are reporting, both patients were females and the age at presentation were 46 and 65 years respectively. The mother probably was harbouring papillary thyroid carcinoma from an earlier age but because of the nature of the disease with slow progression she received attention later in life.

The etiology of thyroid carcinoma is unknown, however, exposure to radiation is a well known factor for the development of thyroid cancer later in life. It may promote the development of cancer in glands already expressing abnormal oncogenes, or it may cause genetic damage and leave the gland susceptible to transformation later by another tumor-promoting agent.

The vertical transmission of FNMTC as in the family we are reporting may imply oncogene activation.

The search for the genes that cause familial non-medullary thyroid cancer syndromes is proving to be not straight forward. Part of the reason is that FNMTC is a non-homogeneous entity unlike MEN₂. One gene for a FNMTC syndrome has been identified, Phosphate and TENs in Homolog (PTEN), which encodes a tumor suppressor. Germline mutations in PTEN have been found in 80% of individuals with classic Cowden syndrome, which is characterized by multiple hamartomas, a high risk of benign and malignant breast carcinoma, follicular and papillary thyroid carcinomas¹⁸.

Table 1: Inherited cancer syndrome where PTC may be a component feature.

Syndrome	Phenotype other than PTC	Chromosomal localization	Gene
PTC-RCC	Papillary RCC	1q21	?
PTC—oxyphilia	Benign thyroid nodules	19p13.2	?
Multinodular goiter	Multinodular goiter	14q31	?
Familial clear cell RCC with PTC	RCC	t(3;8)(p14.2;q24.1)	?
Familial adenomatous polyposis	Colorectal carcinoma, ampullary carcinoma, hepatoblastoma, medulloblastoma	5q21-22	APC
Cowden syndrome ^a	Multiple hamartomas, follicular thyroid carcinoma, benign thyroid nodules, breast cancer, endometrial cancer	10q23.3	PTEN

^a PTC_s have been found in rare Cowden individuals who are germline PTEN mutation negative, although mixed papillary-follicular histologies have been found in families that are PTEN mutation positive.

However, Phosphate and TENs in homolog (PTEN) only accounts for 5% or less of families with breast and papillary thyroid carcinomas (PTC_s) without other features of Cowden syndrome¹⁹. Familial adenomatous polyposis, which predisposes to colorectal carcinoma, is caused by mutations in the APC gene, and PTC is acknowledged as a minor component tumor in this syndrome. However, APC seems to have been excluded as a susceptibility locus in at least some familial PTC families²⁰. Thus, other susceptibility genes for PTC exist.

The first “PTC gene” was localized to 19p13.2 in a single French family with papillary thyroid tumors with cell oxyphilia, which is an unusual type of oncocyctic PTC²¹. A putative locus for multinodular goiter was mapped to 14q 31 in a Canadian Kindred²². In this family, two PTC_s were noted. The majority of other familial PTC families are not linked to either of these two loci²¹⁻²³.

Recently, Malchoff et al²⁴ have found another locus for familial PTC, these investigators have mapped this gene to 1q21 using a multigenerational family segregating PTC and papillary renal cell carcinoma (RCC).

It is apparent that there will be at least 4 susceptible genes for familial PTC. It would seem that familial PTC is a “Catch-all” term that encompasses different syndromes with genetic susceptibility to PTC.

In our patients the genetic analysis has not been done, and taking into account the increased prevalence of the FNMTC, along with high consanguinity in our population, awareness of this syndrome needs to be stressed when dealing with thyroid cancer patients and family screening may be warranted in susceptible cases. However, given the multiple syndromes represented by “Familial PTC” and the likelihood of multiple susceptibility genes, with variable penetrances and expressivity, researchers dedicated to sorting out the genetic etiology of familial PTC may find their work rewarding in the future.

CONCLUSION

This case report we described above supports the existence of inheritance pattern of familial papillary thyroid cancer.

Although the molecular analysis in this family has not been undertaken and it could be argued that the presence of papillary thyroid cancer in this family is an incidental finding. We believe that this family illustrates the need for awareness of the existence of this syndrome and further search among other families is warranted. The recent advances in understanding the molecular basis will make this task much feasible.

REFERENCES

1. Malchoff CD, Malchoff DM. Familial nonmedullary thyroid carcinoma. *Semin Surg Oncol* 1999;16:16-18.

2. Canzian F, Amati P, Harach R, et al. A gene predisposing to familial thyroid tumors with cell oxyphilia maps to chromosome 19p13.2 *Am J Hum Genet* 1998;63:1743-8.
3. Houlston RS, Stratton MR. Genetics of nonmedullary thyroid cancer. *QJ Med* 1995;88:685-93.
4. Loh KC. Familial nonmedullary thyroid carcinoma: a meta-review of case series. *Thyroid* 1997;7:107-13.
5. Fagin JA. Familial nonmedullary thyroid carcinoma: the case for genetic susceptibility. *J Clin Endocrinol Metab* 1997;82:342-8.
6. Lesueur F, Stark T, Tocco T, et al. Genetic heterogeneity in familial nonmedullary thyroid carcinoma: exclusion of linkage to RET, MNG1, and TCO in 56 families. *J Clin Endocrinol Metab* 1999;84:2157-62.
7. Vassilopoulou-Selin R, Palmer L, Tayler S, et al. Incidence of breast carcinoma in women with thyroid carcinoma. *Cancer* 1999;85:696-703.
8. Carl D, Sarfarazi M, Beatriz T, et al. Papillary Thyroid Carcinoma associated with Papillary renal neoplasia: Genetic Linkage Analysis of a distinct heritable tumor syndrome. *J Clin Endocrinol Metab* 2000;85:1758-64.
9. Fearon ER. Human cancer syndromes: Clues to the origin and nature of cancer. *Science* 1997;278:1034-50.
10. Waterhouse J, Muir C, Shanmugaratnam K, et al. Cancer Incidence in five countries, Vol. IV. IARC Scientific publications No. 42. Lyon: International Agency for Research on Cancer, 1982.
11. Woolner LB, Beahrs OH, Black BM, et al. Classification & prognosis of thyroid carcinoma: A study of 885 cases observed in a thirty year period. *AM J Surg* 1961;102:354-387.
12. Vickery AI, Wang CA, Walker AM. Treatment of intrathyroidal papillary carcinoma of the thyroid. *Cancer* 1987;60:2587-95.
13. Smith WG. Familial multiple polyposis: research tools for investigation of the etiology of carcinoma of the colon? *Dis Colon Rectum* 1968;1:17-31.
14. Smith WG, Kern BB. The nature of the mutation in familial multiple polyposis: papillary carcinoma of the thyroid, brain tumors, and familial multiple polyposis. *Dis Colon Rectum* 1973;16:264-71.
15. Carmiel MR, Mute JE, Alexander LL, et al. Association of thyroid carcinoma with Gardner's syndrome in Siblings. *N Engl J Med* 1968;278:1058-9.
16. Robinson DW, Orr TG. Carcinoma of the thyroid and other diseases of the thyroid in identical twins. *Arch Surg* 1955;70:923-8.
17. Borup Christensen S, Ljungberg O, Tibblin S. A Clinical epidemiological study of thyroid carcinoma in Malmö, Sweden *Curr Probl Cancer* 1984;8:1-14.
18. Marsh DJ, Coulon V, Lunetta KL, et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. *Hum Mol Genet* 1998;7:507-15.
19. Marsh DJ, Caron S, Dahia PLM, et al. Germline PTEN mutations in Cowden

- Syndrome –like families. *J Med Genet* 1998;35:881-5.
20. Malchoff CD, Sarfarazi M, Tendler B, et al. Familial papillary thyroid carcinoma is distinct from familial adenomatous polyposis coli. *Thyroid* 1999;9:247-52.
 21. Canzian F, Amati P, Harach R, et al. A gene predisposing to familial thyroid tumors with cell oxyphilia maps to chromosome 19p 13.2. *Am J Hum Genet* 1998;63:1743-8.
 22. Bignell GR, Canzian F, Shayeghi M, et al. Familial nontoxic multinodular goiter locus maps to chromosome 14q, but does not account for familial nonmedullary thyroid cancer. *Am J Hum Genet*. 1997;61:1123-30.
 23. Lesueur F, Stark M, Tocco T, et al. Genetic heterogeneity in familial nonmedullary thyroid carcinoma: exclusion of linkage to RET, MNG1 and TCO in 56 families. *J Clin Endocrinol Metab* 1999;84:2157-62.
 24. Malchoff CD, Sarfarazi M, Tendler B, et al. Papillary thyroid carcinoma associated with papillary renal neoplasia: genetic linkage analysis of a distinct heritable tumor syndrome. *J Clin Endocrinol Metab* 2000;85:1758-64.