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Case Report

Case Report of Familial Non-Medullary Thyroid Carcinoma

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Abstract

Introduction

We report the diagnosis and clinical course of six first-degree relatives with Familial Non-Medullary Thyroid Carcinoma (FNMTC) who displayed genetic anticipation.

Case Presentation

This series follows two twin brothers who presented with neck masses and varying symptoms. Subsequently. their children presented with neck masses at progressively earlier ages.

Management and Outcome

Following the first diagnosed case, each family member underwent Thyroidectomy. Histological analysis revealed papillary carcinoma in 5 cases, 3 of which were follicular variants. The remaining member was found to have benign papillary hyperplasia.

Discussion

The significant FNMTC heritability and genetic anticipation displayed in our case series underscores the vitality of early family screening. Children are generally advised to undergo surgery and radioablation. Genetic testing plays a key role.

Introduction

Non-medullary thyroid cancer represents at least 80% of all thyroid cancer cases in the United States [1]. Approximately 5% of these cases are hereditary, which is known as familial non-medullary thyroid carcinoma (FMNTC) [2]. FNMTC has been recognized only in the last decade or so as a unique clinical entity distinct from the sporadic form. The underlying genetic basis for FNMTC has yet to be established, and studies comparing the clinical course of FNMTC versus its sporadic counterpart ares also inconclusive [2]. However, recent studies indicate that FNMTC might indeed represent a more aggressive entity than previously thought, as evidenced by a higher recurrence rate and reduced disease free survival [3]. We report the diagnosis and clinical course of six first degree relatives with FNMTC who display genetic anticipation.

Patients and Methods

This report is a retrospective chart review of one family that exhibited a strong hereditary pattern of thyroid carcinoma. Some family members had received care at an outside institution and these records were obtained and reviewed with consent. Additionally, interviews were conducted with family members to corroborate details of the family history and identify other relatives who were diagnosed with thyroid disease (Figure 1).

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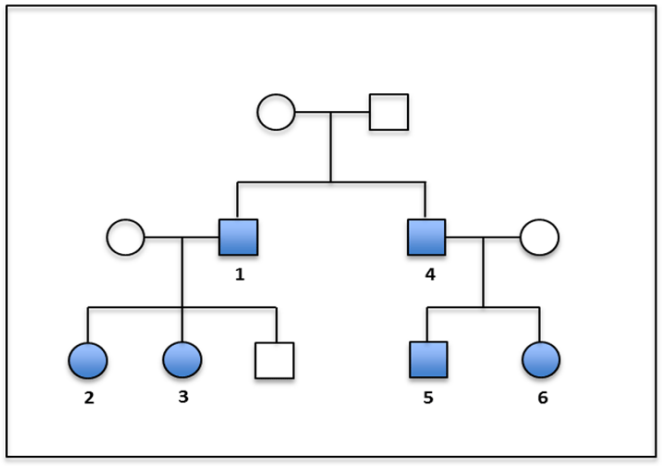

Figure 1. In this pedigree chart, shaded denotes affected family members (patients 1-6).

Case Series

All cases were discussed among a team of pediatric and/or adult endocrinologists. Joint decision making occurred with the family after discussing the risks and harms of treatment versus non-treatment.

Patient-1

Patient 1 is a 43 year old Palestinian-American male who developed a neck mass at the age of 25 (Table 1). At that time, he complained of weight fluctuations, decreased energy level, and periodic dyspnea. A subtotal thyroidectomy was performed and pathology was benign. His clinical symptoms did improve and he remained in reasonably good health. Many years later he developed some neck stiffness and weight gain. Ultrasound revealed multiple left nodules and one enlarged isthmus nodule. He underwent a completion thyroidectomy in August 2013. The pathology demonstrated papillary thyroid microcarcinoma (0.3cm). He did not undergo radioablative iodine due to the small focus of carcinoma.

Table 1: Six patients with familial thyroid disease and clinical features of each. None of the patients exhibited metastasis beyond the lymph nodes.

Patient ID	Relation	Age at Dx	Diagnosis	Multi-focal	Bilateral	Lymph node involvement
1	Index patient	27	Papillary thyroid microcarcinoma	X		
2	Older daughter of patient 1	12	Angioinvasive follicular variant of papillary thyroid carcinoma	X	X	
3	Younger daughter of patient 1	9	Follicular variant of papillary thyroid carcinoma			
4	Identical twin of patient 1	43	Papillary thyroid carcinoma	X		X
5	Son of patient 4	13	Benign papillary hyperplasia	X	X	
6	Daughter of patient 4	8	Follicular variant of papillary thyroid carcinoma			

Patient-2

Patient 2 is the elder daughter of patient 1 and presented to our clinic in February 2013 at the age of 12 with an asymptomatic goiter. On exam, she was found to have a 3cm left-sided neck mass that was mobile, smooth, and non-tender. An ultrasound revealed a multi-nodular goiter with the left side larger than the right. Due to the size of the primary lesion, bilateral disease, and strong family history, a total thyroidectomy was performed in April 2013 followed by radioactive iodine ablation. Pathologic diagnosis revealed angioinvasive follicular variants of papillary carcinoma of the left and right thyroid lobe, confined to the thyroid gland.

Patient-3

Patient 3 is the younger daughter of patient 1. At age 9 she developed an asymptomatic swelling on the right side of her neck. Ultrasound confirmed a 1.5cm right-sided thyroid nodule. FNA analysis could not rule out follicular variant of papillary thyroid carcinoma, and thus excision of the nodule was recommended.

Due to the family history of thyroid cancer her parents elected for a right hemithyroidectomy, which was performed in April 2012. Pathology revealed a tan, soft, fleshy nodule in the inferior pole of the lobe measuring 2.5 x 2.0 x 1.9 cm (Figure 2A). It was originally diagnosed as follicular adenoma.

She was closely followed and had an uneventful post-operative course. In April 2013, after her sister (Patient 2) was diagnosed with papillary carcinoma, Patient 3's pathologic specimen was re-examined by an outside lab specializing in thyroid disease. This second evaluation found that the atypia was sufficiently severe to warrant the diagnosis of follicular variant of papillary carcinoma (Figure's 2B-D). She then underwent a successful completion thyroidectomy followed by radioactive iodine ablation.

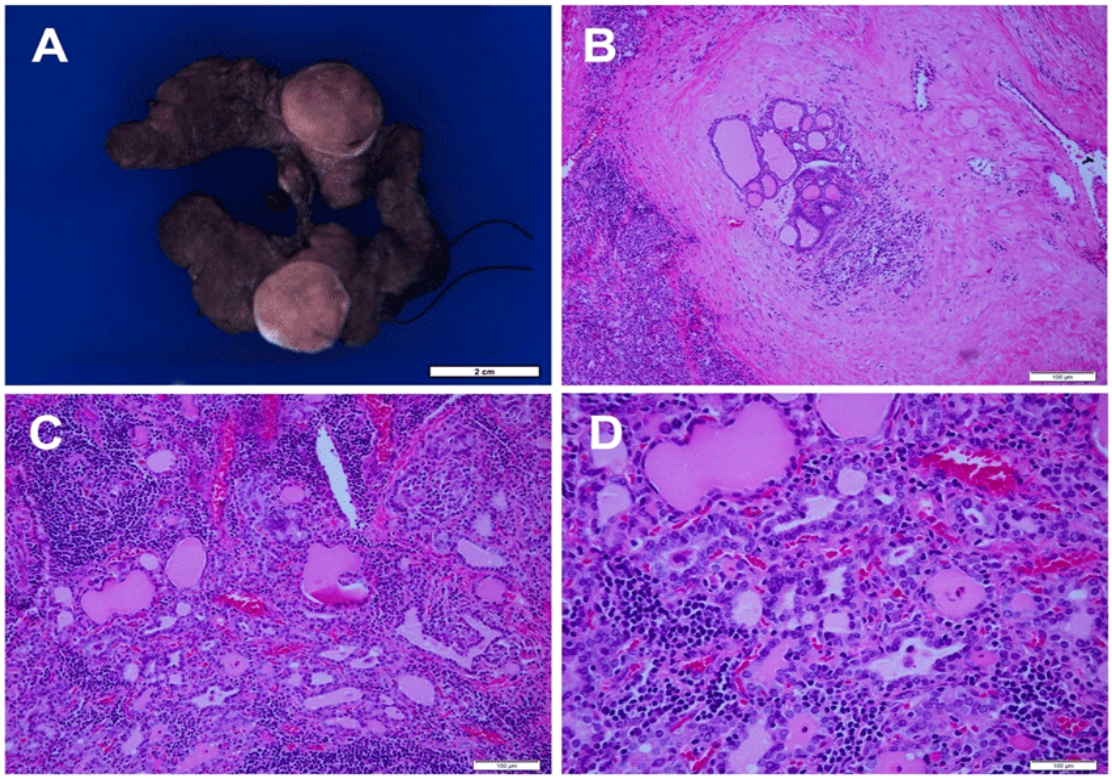

Figure 2. *Histological findings of neck mass in Patient 3. (A) Gross pathology demonstrates a 2.5 x 2.0 x 1.9 cm tan, fleshy nodule. (B) Histopathology reveals a focus of papillary carcinoma surrounded by dense fibrosis, as well as (C) disruption of follicular architecture and infiltrating mononuclear cells. (D) A microfollicular growth pattern with characteristic nuclear features of papillary carcinoma (nuclear grooves, ground glass appearance, chromatin clearing) suggests follicular variant of papillary thyroid carcinoma.*

Patient-4

Patient 4 is the identical twin brother of patient 1. He presented to his primary care provider in January 2014 with a 1-2 year history of cold intolerance, 25lb of unexpected weight gain, increased moodiness and depression, as well as neck fullness. Of note, he has worked as a medical dosimetrist for a radiation oncology practice for 23 years.

A neck ultrasound revealed heterogenous enlargement of the thyroid with multiple nodules, including one in the mid pole of the right lobe that contained calcifications. Total thyroidectomy was recommended given his strong family history and worrisome ultrasound findings. FNA was not recommended as a negative result would not completely rule out thyroid cancer. He underwent total thyroidectomy with central lymph node dissection in February 2014. Pathology revealed multifocal papillary thyroid carcinoma with 8 of 12 positive nodes. He did not receive radioactive iodine ablation. He did experience some hoarseness post-operatively that resolved, but otherwise his course

has been uneventful. He has been closely monitored by his endocrinologist.

Patient-5

Patient 5 is the son of patient 4 who presented at age 13 with a 1 cm mobile mass within the thyroid isthmus. Ultrasound revealed a semi-solid mass with a fluid filled pocket. After detailed discussions, the parents strongly desired a total thyroidectomy due to the extensive family history. This revealed multiple cystic nodules bilaterally. This was diagnosed as benign papillary hyperplasia, with insufficient atypical to warrant a diagnosis of papillary carcinoma. A second opinion was sought by an outside lab which agreed with the original diagnosis.

Patient-6

Patient 6 is the daughter of patient 4. She has a history of nephroma which was surgically resected at 6 months of age. She presented to our clinic in November 2013 at the age of 8 years old because of an asymptomatic 1.5cm midline neck mass identified on routine physical exam by her family physician. She underwent total thyroidectomy followed by radioactive iodine ablation. Pathology revealed follicular variant of papillary carcinoma

Discussion

Approximately 5-15% of cases of non-medullary thyroid carcinoma are familial and have a genetic tendency [4]. FNMTC is defined as involvement of three or more first-degree relatives, while less than three statistically suggests sporadic etiologies [5]. Studies have demonstrated that the risk of developing NMTC is 5 to 9 times higher in individuals with an affected first-degree relative than in the general population [4,6]. Three forms of inheritance are identified: parent/offspring, sibling, and parent/offspring/sibling.12Diagnoses in men and children are more likely to be familial [5].

Though genetic testing would have been interesting in this case series, studies on possible genetic mutations were not obtained at the request of the family. A definitive causative gene of FNMTC has not yet been established, but there is strong evidence supporting a genetic lineage. It is currently believed to be autosomal dominant with incomplete penetrance and variable expressivity [5]. Variants with high frequency and low penetrance are increasingly supported by recent data to be the leading genetic risk factor [7]. While the BRAF mutation has been associated in about 40% of the sporadic papillary carcinoma, only one study found a similar prevalence in FNMTC [8]. On the other hand, an increased risk was found in a European population with chromosomes 9p22.23 and 14q13.3 with downstream thyroid transcription factors FOXE1 and NKX2-1 [8]. Other susceptible genes, though largely not validated further, include MNG1, TCO, fPTC/PRN, and SRGAP1 [9]. Another study linked FNMTC1 syndrome and chromosome 2q21, as well as familial PTC with renal papillary neoplasia and chromosome 1q21 [8]. Other syndromic relationships confirmed by molecular genetics include PTEN hamartoma syndrome (Cowden), Familial Adenomatous polyposis, McCune Albright, Wermer, and MEN2A. Less established conditions includePeutz-Jeghers, ataxia-telangiectasia, Li-Fraumeni, and DICER1 syndromes are less established [8,5]. Non-syndromic disorders include pure fPTC with or without oxyphilia and fPTC with multinodular goitre [5]. Our case series demonstrated a likely dominant and pure variant.

Studies comparing clinical features and aggressiveness of FNMTC versus sporadic NMTC are conflicting and inconclusive. One study demonstrated clinical anticipation in FNMTC in which cancer in the second generation presented at a significantly younger age and was more advanced at time of diagnosis, suggesting a complex genetic basis to the disease [10]. A large Japanese study of 258 FNMTC cases showed that these patients tended to display a greater degree of intraglandular dissemination (40.7% vs 28.5%) and recurrence (16.3% vs 9.6%) compared to patients with sporadic NMTC, suggesting worse prognosis [11]. However, the more frequent recurrences were limited to the local lymph nodes, and thus readily treatable. Thus, although disease-free survival was lower in FNMTC, overall survival remained the same [11]. Another large study found FNMTC to be more aggressive than the sporadic form, particularly in families with 3 or more affected members. However, there was no difference in overall life expectancy [12]. A recent systematic review and meta-analysis comparing FNMTC to its sporadic counterpart revealed a predisposition to multicentric, bilateral disease, local invasion, extrathyroidal extension, lymph node metastases, and reduced disease-free survival in FNMTC patients [3]. FNMTC is a heterogeneous disease showing diverse natural histories, which may account for the conflicting clinical data as well as lack of common genetic findings in this disease.

There is no difference in the histology of familial papillary carcinoma and the sporadic form. Surgery is the treatment of choice for non-medullary thyroid cancer. Thyroid lobectomy may be sufficient for small (<1cm), low-risk, unifocal, intrathyroidal papillary or follicular thyroid carcinomas in the absence of prior head and neck irradiation or clinically involved cervical node metastasis. For larger tumors more than 1cm, lobectomy resulted in higher incidence of recurrence and death. Total thyroidectomy is preferred in these cases [13].

For children diagnosed with papillary thyroid carcinoma, the American Thyroid Association (ATA) recommends total thyroidectomy as long term analysis shows decreased risk for persistent/recurrent disease [14]. Furthermore, radioactive iodine ablation should be used selectively in children who will benefit the most. Such patients include those with unresectable disease and iodine-avid distant metastases, particularly T3 or extensive regional nodal involvement [14,15]. Those

with pulmonary metastases may actually have therapeutic benefits from 131I threatment [15]. For follow-up, neck ultrasound is recommended at 6-12 month intervals for at least 5 years. Thyroglobulin levels should be routinely monitored as well, as this is a highly sensitive tumor marker of differentiated thyroid carcinoma in children, even in those who did not undergo radioactive iodine ablation.

In regard to medullary thyroid carcinoma (MTC), the ATA, total thyroidectomy and neck dissection is also recommended for all stages, followed by thyroid hormone therapy. In contrast, radioactive iodine is ineffective due to decreased uptake by MTC cells. External beam radiation therapy may be used to reduce recurrence for extensive stage III and IV tumors or when complete resection is not possible. Lastly, testing for other neoplasms associated with MEN2 syndromes is recommended, such as pheochromocytomas and parathyroid carcinomas [16].

Family members should undergo ultrasound surveillance as this has been shown to detect tumors at a smaller initial size and with a lower incidence of metastasis [14]. Quality of life in these patients, especially children, may be affected and should be monitored closely. Indeed, our case series demonstrates the significant heritability of FNMTC and the genetic anticipation displayed herein underscores the importance of early family screening.

Conclusion

5-15% of non-medullary thyroid carcinoma cases are familial. FNMTC may or may not be more aggressive than the sporadic form. The generally advised treatment for FNMTC is total thyroidectomy with close follow-up, and family members should be closely screened beginning at a young age. Children diagnosed with any form of thyroid carcinoma should undergo total thyroidectomy and radioactive iodine ablation should be used in children who would benefit the most. They should be monitored for recurrence with periodic neck ultrasound, thyroglobulin levels, and thyroid function tests.

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