Original Article

Clinicopathologic Features of Familial Nonmedullary Thyroid Carcinoma

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Abstract

Background: Familial nonmedullary thyroid carcinoma (FNMTC) is a variant of nonmedullary thyroid carcinoma(NMTC) with particular clinicopathologic features. In recent years, a number of studies have shown that FNMTC is more invasive than sporadic NMTC(SNMTC). The purpose of this study was to explore the differences in clinicopathologic features of FNMTC between different types of families and to determine in which of these families more invasive FNMTC occurred.

Methods: We retrospectively reviewed all patients with thyroid carcinoma admitted to Peking Union Medical College Hospital from January 2009 to July 2013 in the database. Of all 2000 cases, 55 met the inclusive criteria for FNMTC and were studied. There are two different grouping methods. The first is that all samples were allocated to families with three or more first-degree relatives affected (FNMTC-3 group) and families with only two affected first-degree relatives (FNMTC-2 group). The second is that all patients were divided into families with three or more affected first-degree relatives over two generations (FNMTC-3-2 group) and the other families. We compared the clinicopathologic features such as sex, age, tumor size, multifocality, location, complications by thyroiditis, complications by benign thyroid nodules, surgical procedure, capsule invasion, histological type, lymph node metastases, tumor node metastasis stage, and BRAF mutation between FNMTC-2 group and FNMTC-3 group. We also made the same comparison between FNMTC-3-2 group and other families.

Results: No pronounced differences in clinicopathological features were present between FNMTC-2 group and FNMTC-3 group. The proportion of FNMTC-3-2 group aged <45 years was significantly higher than that in the other families (58.8% vs. 26.3%, $P = 0.021$). A similar difference was found in the proportion of lymph node metastasis (64.7% vs. 34.2%, $P = 0.035$).

Conclusions: FNMTC-3-2 is more invasive than the other families. Early screening and positive treatment for members of these families are recommended.

Key words: Clinical Pathology; Familial; Nonmedullary; Thyroid Carcinoma

Introduction

Nonmedullary thyroid carcinoma (NMTC) is an endocrine-related cancer which originates from follicular epithelial cells, including papillary thyroid carcinoma, follicular thyroid carcinoma, and anaplastic thyroid carcinoma. NMTC is mostly sporadic, but familial clustering is described in 3.5–10.0% of all cases, referred to as familial NMTC (FNMTC).[1-6] FNMTC is defined as NMTC in a patient with two or more first-degree relatives who have been diagnosed with differentiated thyroid cancer (DTC) of follicular cell origin and have no other familial syndrome or radiation exposure history.[7] FNMTC is more invasive than sporadic NMTC (SNMTC) and has a worse prognosis,[8-11] suggesting that the severity of NMTC is related to hereditary factors. Some studies have found that in families with two affected first-degree relatives (FNMTC-2), 62–69% are sporadic cases, whereas in families with three or more affected first-degree relatives (FNMTC-3), fewer than 6% have one or more sporadic case.[12] The aim of this study was to explore differences in clinicopathologic features between FNMTC-3 and FNMTC-2 and to determine in which type of family more invasive NMTC occur.

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Methods

All patients with thyroid carcinoma who had been admitted to Peking Union Medical College Hospital (PUMCH) from January 2009 to July 2013 in the database were reviewed retrospectively. The inclusive criteria for FNMTC are DTC

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of follicular cell origin confirmed by surgical pathology in PUMCH with two or more first-degree relatives (parents, children, and siblings) affected. Of all 2000 cases, 68 met the inclusive criteria for FNMTC based on the family history of thyroid cancer in medical record. Of these, 13 patients were excluded according to the exclusive criteria: Coexistence of syndromes associated with the development of thyroid cancer, a history of radiation exposure, or incomplete data. Thus, 55 cases were eligible for the study.

Data collection

Relevant general and clinical data of all studied cases were extracted from the PUMCH database. The clinicopathologic features such as sex, age, symptom, tumor size, multifocality, location, complications by thyroiditis, and complications by benign thyroid nodules, surgical procedure, capsule invasion, histological type and subtype, lymph node metastases, tumor node metastasis stage, and BRAF mutation between different groups were recorded. BRAF mutations were checked by a real-time fluorescent polymerase chain reaction technique and the pathological subtypes of samples from all studied families were classified using reserved paraffin specimens.

Groupings

There are two different grouping methods. The first is that all samples were allocated to FNMTC-3 group and FNMTC-2 group. The second is that all patients were divided into families with three or more affected first-degree relatives over two generations (FNMTC-3-2 group) and the other families. We compared the clinicopathologic features between FNMTC-3 group and FNMTC-2 group. The same comparison was also made between FNMTC-3-2 group and the other families.

Statistical analysis

All categorical variables were presented as the sum and percentage of subjects. χ^2 test was used to assess the differences among different groups. In all cases, a $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

All the research methods and investigational tools in this study were approved by the Ethics Committee of PUMCH. All the subjects gave a written informed consent and consented to the publication of the data.

Results

Relevant clinical variables and clinicopathologic features of enrolled patients

All 55 cases in 27 families underwent surgical treatment, and all diagnoses of NMTC were confirmed by pathologic examination of resected specimens. There were 23 patients in 15 families with FNMTC-2 and 32 patients in 12 families with FNMTC-3, 17 of whom (seven families) with FNMTC-3-2. Fifty-three patients (96.4%) underwent total thyroidectomy and central compartment lymph node dissection. Among them, 48 patients (87.3%) underwent this operational procedure during the initial surgery, and others underwent a second (7.3%) or a third operation (1.8%) because of recurrent lymph node metastases. Of the remaining two patients, one underwent total tumor-bearing thyroidectomy and contra-lateral partial resection and the other underwent bilateral subtotal thyroidectomy (a nodular goiter had been diagnosed on the intraoperative frozen section; the postoperative pathological diagnosis was thyroid microcarcinoma). No patient developed recurrent laryngeal nerve injury or permanent hypoparathyroidism. The duration of postoperative follow-up ranged from 2 to 117 months (mean, 33.8 months), during which there were no metastases or deaths. Details are shown in Table 1.

Table 1: Clinicopathologic data of 55 patients with FNMTC

Variables	*n* (%)
Gender	
Male	13 (23.6)
Female	42 (76.4)
Age (years) (mean, 46.74 ± 8.16)	
<45	20 (35.8)
≥45	35 (64.2)
Asymptomatic preoperatively	48 (87.3)
Complications by thyroiditis	18 (32.7)
Complications by benign thyroid nodules	19 (34.5)
Tumor size (cm) (mean, 1.02 ± 1.01)	
<1	17 (30.9)
≥1	38 (69.1)
Bilateral or multifocal	21 (38.2)
Location	
Upper	13 (15.7)
Middle	54 (65.1)
Lower	14 (16.7)
Isthmus	2 (2.4)
Surgical procedure	
Total thyroidectomy and lymph node dissection of center group	53 (96.4)
Bilateral subtotal thyroidectomy or total tumor-bearing thyroidectomy and contralateral partial resection	2 (3.6)
Capsule invasion	17 (30.9)
Histological type	
Papillary thyroid carcinoma	55 (100.0)
Classical variant	53 (96.4)
Special types	2 (3.6)
Solid variant	1(1.8)
Solid sclerosing with Warthin-like variant	1
Lymph node metastases	24 (43.6)
TNM stage	
I	34 (61.8)
II	0 (0)
III	18 (32.7)
IV	3 (5.5)
Two or more operations	6 (10.9)
BRAF mutation	47 (85.5)

TNM: Tumor node metastasis; FNMTC: Familial nonmedullary thyroid carcinoma.

Clinicopathological features and prognosis according to category

All 55 cases are diagnosed as papillary thyroid carcinoma, of which 53 were classical variants, one was a solid variant and one was a solid sclerosing with Warthin-like variant. There were no pronounced differences in clinicopathological features between FNMTC-2 group and FNMTC-3 group. However, the proportion of lymph node metastasis was 53.1% in FNMTC-3 group. Comparison of FNMTC-3-2 group with the other families showed significant differences in the ratio of patients aged <45 years (58.8% vs. 26.3%, $P = 0.021$) and lymph node metastasis (64.7% vs. 34.2%, $P = 0.035$). However, there were no significant differences between these two groups in other clinicopathologic features such as multifocality (52.9% vs. 31.6%), local invasion (29.4% vs. 31.6%), reoperation (17.6% vs. 7.9%), and BRAF mutation (94.1% vs. 81.6%) [Figure 1]. The details are shown in Table 2.

Discussion

Familial nonmedullary thyroid carcinoma is a variant of NMTC with particular clinicopathologic features. In recent years, a number of studies have shown that FNMTC is more invasive than SNMTC in terms of multi-foci, capsule invasion, lymph node metastasis, rate of the second surgery and overall survival rate.[8-11,13] It is commonly reported that FNMTC accounts for 3.5–10.0% of thyroid carcinomas.[1,2] The proportion of 3.4% found in this study is corresponding with previously reported.

The average age of onset for FNMTC is 39–43 years, which is 6–7 years younger than for SNMTC (46–49 years).[2,3,8] The reason may be that the inherited form of the disease develops earlier than the spontaneous form or that after one family member has been diagnosed, the diagnosis is made earlier in subsequent family members. The average age of onset in this group was 46.74 years, which is older than reported. This apparent discrepancy may be attributable to the comparative small numbers of patients in this study and the bias of hospital choice (i.e., many younger patients in China, especially children with suspicious thyroid nodules, select specialized hospitals to get treatment).

In general, 22.5–30.0% of thyroid carcinomas are multifocal;[14,15] however, 33.6–48.0% of FNMTCs are multifocal.[11,16,17] In this study, the rate was 38.2%, which is consistent with other reports. A relatively high rate of multifocality is one of the main features of FNMTC.

In addition to distant metastasis, lymph node metastasis is another independent risk factor affecting the prognosis of thyroid carcinoma. The survival rate at 14 years in DTC patients with lymph node metastasis is reportedly 79%, which is lower than that without such metastasis (82%).[18] The lymph node metastasis rate of DTC is reported greatly different in different studies. A key contributing factor may be the selection of surgical procedure.

Thorough lymph node dissection may result in the identification of more lymph node metastases, which can change the pathological stage. Although the surgical procedures differ, most studies comparing FNMTC with SNMTC have reported that the lymph node metastasis rate is 4–57% in FNMTC, which is higher than the counterpart in SNMTC (5–38%).[3,5] In our study, almost 70% of patients had microcarcinomas, and the lymph node metastasis rate was 43.6%. This high rate may be attributable to the performance of total thyroidectomy and the dissection of central lymph nodes in most cases. Thus, this rate may be approaching the real rate of lymph node metastasis in patients with FNMTC. To improve efficacy, reduce recurrence, and avoid repeat surgery, we recommend proactive treatment protocols, including radical surgical procedures.[19] In our study, because of the high rate of initial total thyroidectomy and dissection of central lymph nodes, only six patients (11.3%) required two or more operations for partial recurrence or lymph node metastasis.

The BRAF mutation does not cause FNMTC;[20,21] however, it may be associated with low efficacy of ^{131}I treatment and

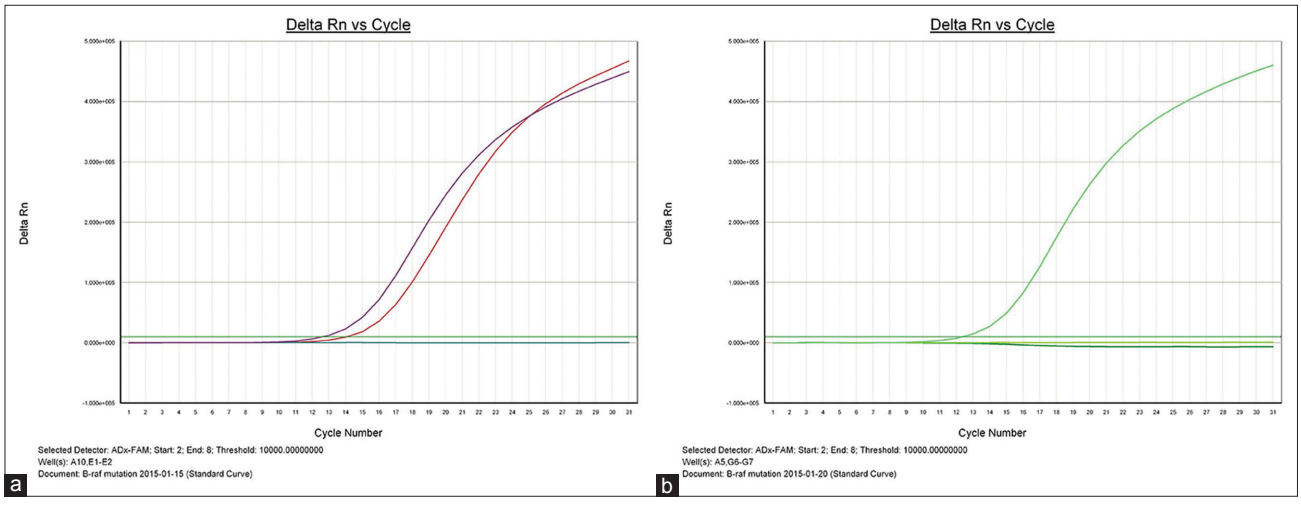

Figure 1: (a) BRAF mutation is detected and; (b) No BRAF mutation is found.

Table 2: Comparison of clinicopathological features of different family types (*n* (%))

Variable	FNMTC-2 group* (*n* = 23)	FNMTC-3 group* (*n* = 32)	*P*	FNMTC-3-2 group* (*n* = 17)	The other families* (*n* = 38)	*P*
Gender						
Male	3 (13.0)	10 (31.2)	0.117	6 (35.3)	7 (18.4)	0.339
Female	20 (87.0)	22 (68.8)		11 (64.7)	31 (81.6)	
Age (years)						
<45	6 (26.1)	14 (43.8)	0.179	10 (58.8)	10 (26.3)	0.021
≥45	17 (73.9)	18 (56.2)		7 (41.2)	28 (73.7)	
Complications by thyroiditis						
Yes	7 (30.4)	11 (34.4)	0.759	7 (41.2)	11 (28.9)	0.372
No	16 (69.6)	21 (65.6)		10 (58.8)	27 (71.1)	
Complications by benign thyroid nodules						
Yes	11 (47.8)	8 (25.0)	0.099	7 (41.2)	12 (31.6)	0.489
No	12 (52.2)	24 (75.0)		10 (58.8)	26 (68.4)	
Tumor size (cm)						
>1	7 (30.4)	10 (31.3)	0.949	6 (35.3)	11 (28.9)	0.638
≤1	16 (69.6)	22 (69.7)		11 (64.7)	27 (71.1)	
Location (83)						
Upper	6 (18.2)	7 (14.0)	0.451	3 (11.5)	9 (15.8)	0.080
Middle	20 (62.5)	34 (68.0)		19 (73.1)	36 (63.2)	
Lower	7 (21.2)	7 (14.0)		2 (7.7)	12 (21.1)	
Isthmus	0 (0)	2 (4.0)		2 (7.7)	0 (0)	
Number of operations						
1	21 (91.3)	28 (87.5)	1.000	14 (82.4)	35 (92.1)	0.359
≥2	2 (8.7)	4 (12.5)		3 (17.6)	3 (7.9)	
Multifocality						
Yes	9 (39.1)	12 (37.5)	0.902	9 (52.9)	12 (31.6)	0.132
No	14 (60.9)	20 (62.5)		8 (47.1)	26 (68.4)	
Capsule invasion						
Yes	6 (26.1)	11 (34.4)	0.512	5 (29.4)	12 (31.6)	0.872
No	17 (73.9)	21 (65.6)		12 (70.6)	26 (68.4)	
Lymph node metastases						
Yes	7 (30.4)	17 (53.1)	0.094	11 (64.7)	13 (34.2)	0.035
No	16 (69.6)	15 (46.9)		6 (35.3)	25 (65.8)	
TNM stage						
I	16 (69.6)	18 (56.3)	0.605	10 (58.8)	24 (63.2)	0.954
II	0 (0)	0 (0)		0 (0)	0 (0)	
III	6 (26.1)	12 (37.5)		6 (35.3)	12 (31.6)	
IV	1 (4.3)	2 (6.2)		1 (5.9)	2 (5.3)	
BRAF mutation						
Yes	20 (87.0)	27 (84.4)	1.000	16 (94.1)	31 (81.6)	0.223
No	3 (13.0)	5 (15.6)		1 (5.9)	7 (18.4)	

*FNMTC-2 group: families with only two affected first-degree relatives; FNMTC-3 group: families with three or more affected first-degree relatives; FNMTC-3-2 group: families with three or more affected first-degree relatives over two generations; The other families: families who did not meet the criteria of FNMTC-3-2 group. TNM: Tumor node metastasis; FNMTC: Familial nonmedullary thyroid carcinoma.

poor prognosis in patients with DTC. The mutation rate reportedly ranges from 54.4% to 73.4% in DTCs.[22-24] In our study, 47 patients (85.5%) had the BRAF mutation. Such a high rate may indicate a worse prognosis of FNMTC and further justifies proactive surgery for these patients.

The rate of invasiveness of FNMTCs was similar in FNMTC-2 group and FNMTC-3 group. However, FNMTC-3 group had higher rate of distant metastasis (13.5% vs. 5.5%), reoperation (15.4% vs. 3.6%), and death (3.1% vs. 1.8%) than FNMTC-2 group.[16] Studies with larger samples and longer follow-up periods are needed to confirm our findings.

As the general principles of genetics indicate hereditary factors are likely involved in a disease with familial aggregation over two generations. Therefore, it is safe to presume that FNMTC-3-2 is more likely to be genuine FNMTC.

So far, no other published studies have investigated the clinicopathologic differences between FNMTC-3-2 and other FNMTCs. In our study, the ratio of FNMTC-3-2 aged <45 years was significantly higher than that in the other families (58.8% vs. 26.3%). A similar difference was found in the ratio of lymph node metastasis (64.7% vs. 34.2%,).

The rate of multifocality (52.9%) and BRAF mutation (94.1%) was quite high in FNMTC-3-2. These trends suggest the disease is more invasive in FNMTC-3-2. Screening of FNMTC-3-2 may enable identification of patients with unique genetic and clinical features, and active treatments for suspicious patients in these families are recommended.

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