Clinicopathologic Features of Familial Nonmedullary Thyroid Carcinoma

Yu-Fang Fan¹, Bo Zhang², Xiao Yang², Zhong-Hua Shang³, Hong-Feng Liu¹, Yong Xie¹, Yue-Wu Liu¹, Wei-Sheng Gao¹, Qiong Wu², Xiao-Yi Li¹

¹Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
²Department of Ultrasound, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China
³Department of General Surgery, Second Clinical Hospital of Shanxi Medical University, Taiyuan, Shanxi 030001, China

Background: Familial nonmedullary thyroid carcinoma (FNMT) is a variant of nonmedullary thyroid carcinoma (NMTC) with particular clinicopathologic features. In recent years, a number of studies have shown that FNMT is more invasive than sporadic NMTC (SNMTC). The purpose of this study was to explore the differences in clinicopathologic features of FNMT between different types of families and to determine in which of these families more invasive FNMT 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 FNMT 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 (FNMT-3 group) and families with only two affected first-degree relatives (FNMT-2 group). The second is that all patients were divided into families with three or more affected first-degree relatives over two generations (FNMT-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 FNMT-2 group and FNMT-3 group. We also made the same comparison between FNMT-3-2 group and other families.

Results: No pronounced differences in clinicopathological features were present between FNMT-2 group and FNMT-3 group. The proportion of FNMT-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: FNMT-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 (FNMT).¹⁻⁶ FNMT 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.¹⁷ FNMT is more invasive than sporadic NMTC (SNMTC) and has a worse prognosis,¹⁸⁻¹¹ suggesting that the severity of NMTC is related to hereditary factors. Some studies have found that in families with two affected first-degree relatives (FNMT-2), 62–69% are sporadic cases, whereas in families with three or more affected first-degree relatives (FNMT-3), fewer than 6% have one or more sporadic case.¹² The aim of this study was to explore differences in clinicopathologic features between FNMT-3 and FNMT-2 and to determine in which type of family more invasive NMTC occur.

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 FNMT are DTC
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 FNMTT 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 FNMTT-3 group and FNMTT-2 group. The second is that all patients were divided into families with three or more affected first-degree relatives over two generations (FNMTT-3-2 group) and the other families. We compared the clinicopathologic features between FNMTT-3 group and FNMTT-2 group. The same comparison was also made between FNMTT-3-2 group and the other families.

Statistical analysis
All categorical variables were presented as the sum and percentage of subjects. \( \chi^2 \) 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 FNMTT-2 and 32 patients in 12 families with FNMTT-3, 17 of whom (seven families) with FNMTT-3-2. Fifty-three patients (96.4%) 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 FNMTT

| 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) | 2 (2.4)    |
| 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; FNMTT: 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 FNMC-2 group and FNMC-3 group. However, the proportion of lymph node metastasis was 53.1% in FNMC-3 group. Comparison of FNMC-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 FNMC is more invasive than SNMTC in terms of multi-foci, capsule invasion, lymph node metastasis, rate of the second surgery and overall survival rate. It is commonly reported that FNMC accounts for 3.5–10.0% of thyroid carcinomas. The proportion of 3.4% found in this study is corresponding with previously reported. The average age of onset for FNMC is 39–43 years, which is 6–7 years younger than for SNMTC (46–49 years). 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; however, 33.6–48.0% of FNMCs are multifocal. 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 FNMC.

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 with such metastasis (82%). 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 FNMC with SNMTC have reported that the lymph node metastasis rate is 4–57% in FNMC, which is higher than the counterpart in SNMTC (5–38%). 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 FNMC. To improve efficacy, reduce recurrence, and avoid repeat surgery, we recommend proactive treatment protocols, including radical surgical procedures.

BRAF mutation does not cause FNMC; however, it may be associated with low efficacy of \(^{131}\)I treatment and...
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%).

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

| Variable                                | FNMT-2 group* (n = 23) | FNMT-3 group* (n = 32) | P     | FNMT-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)                       | 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)                    |       |

*FNMT-2 group: families with only two affected first-degree relatives; FNMT-3 group: families with three or more affected first-degree relatives; FNMT-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 FNMT-3-2 group. TNM: Tumor node metastasis; FNMTC: Familial nonmedullary thyroid carcinoma.
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.

References

1. Stoffer SS, Van Dyke DL, Bach JV, Szpunar W, Weiss L. Familial papillary carcinoma of the thyroid. Am J Med Genet 1986;25:775-82.
2. Moses W, Weng J, Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. Thyroid 2011;21:367-71.
3. Mazeh H, Benavidez J, Poehls JL, Youngwirth L, Chen H, Sippel RS. In patients with thyroid cancer of follicular cell origin, a family history of nonmedullary thyroid cancer in one first-degree relative is associated with more aggressive disease. Thyroid 2012;22:3-8.
4. Park YJ, Ahn HY, Choi HS, Kim KW, Park do J, Cho BY. The long-term outcomes of the second generation of familial nonmedullary thyroid carcinoma are more aggressive than sporadic cases. Thyroid 2012;22:356-62.
5. Grossman RF, Tu SH, Duh QY, Siperstein AE, Novosolov F, Clark OH. Familial nonmedullary thyroid cancer. An emerging entity that warrants aggressive treatment. Arch Surg 1995;130:892-7.
6. Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, et al. Increased risk for nonmedullary thyroid cancer in the first-degree relatives of prevalent cases of nonmedullary thyroid cancer: A hospital-based study. J Clin Endocrinol Metab 2001;86:5307-12.
7. Sturgeon C, Clark OH. Familial nonmedullary thyroid cancer. Thyroid 2005;15:588-93.
8. Alsanea O, Wada N, Ain K, Wong M, Taylor K, Ituarte PH, et al. Familial nonmedullary thyroid carcinoma displays the features of clinical anticipation suggestive of a distinct biological entity. Endocr Relat Cancer 2008;15:207-15.
9. Xing M. The T1799A BRAF mutation is not a germline mutation in familial nonmedullary thyroid cancer. Clin Endocrinol (Oxf) 2005;63:263-6.
10. Kim SW, Lee JI, Kim JW, Ki CS, Oh YL, Choi YL, et al. BRAFV600E mutation analysis in fine-needle aspiration cytology specimens for evaluation of thyroid nodule: A large series in a BRAFV600E-prevalent population. J Clin Endocrinol Metab 2010;95:3693-700.
11. Rusinek D, Gubala E. BRAF initiating mutations in the papillary thyroid carcinoma. Endokrynol Pol 2006;57:438-44.
12. Kim TY, Kim WB, Rhee YS, Song JY, Kim JM, Gong G, et al. The BRAF mutation is useful for prediction of clinical recurrence in low-risk patients with conventional papillary thyroid carcinoma. Clin Endocrinol (Oxf) 2006;65:364-8.

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