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Familial Non Medullary Thyroid Cancer: Clinic Cases and Review of literature

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Abstract

About 95% of non-medullary thyroid tumors arise from follicular cells and about 3.5 to 6.2% of these fall within the group of non-medullary thyroid cancer families (Familial non-medullary thyroid cancer FNMTC), and represent a class of neoplastic syndrome. The cause of FNMTC is suspected to be an autosomal dominant trait with incomplete penetrance, although it is not possible to exclude a polygenic trait. The strong association between goitre and papillary thyroid cancer even in cases without familiarity, tends to assume that the multinodular goitre associated with papillary thyroid cancer (PTC) is not only a familial syndrome, but probably in multinodular goiter there is a transformation of thyroid epithelial malignancy cells. The inclusion criteria for FNMTC was identified in primary inclusion criteria: 1) thyroid cancer in two or more first degree relatives, 2) multinodular goiter in three or more first or second degree relatives; secondary inclusion criteria: 1) early thyroid cancer, 2) multifocal and / or bilateral tumor, 3) invasion of the tumor tissue surrounding the thyroid, and 4) benign thyroid disease in young patients of the same family. The hereditary predisposition to FNMTC exists if two primary criteria are satisfied or one primary criteria and three secondary criteria are satisfied.

Exclusion criteria are 1) exposure to radiation; 2) presence of neoplastic syndromes. If in a family there are two relatives with thyroid cancer the risk that members of the same family develop thyroid cancer is between 31% and 53%, and if there are three relatives with thyroid cancer risk increases to over 95%. The early presentation and highly aggressive FNMTC justify early screening about ten years earlier than the general population. In subjects at risk for FNMTC with suspicious nodules surgery is well advised and in the case of pre-operative, intra-or postoperative diagnosis of PTC it is correct to adopt an aggressive treatment (total thyroidectomy + VI level lymphadenectomy followed by radioiodine therapy and hormone suppression therapy) in order to counter the aggressive behavior of FNMTC. Those small families with strong evidence for susceptibility to goitre / papillary thyroid cancer even though they don't fall within the criteria for inclusion in FNMTC should also be included.

Keywords: Familial non-medullary thyroid cancer, Diagnoses, Treatment, Follow-up

Case 1

A woman of 28, with absence of comorbidity, family history negative for thyroid disease, was in treatment at our out-patients surgery for Hashimoto's thyroiditis with levothyroxine. The sonographic follow-up in May 2011 revealed the presence of a suspicious lump. The patient underwent FNAB (type 5) with bilateral cervical-lymphadenopathy suspicious for disease. The patient underwent total thyroidectomy en bloc. Histological examination of frozen sections diagnosed papillary carcinoma. As per protocol was performed dissection of the sixth cervical level and laterocervical lymphadenectomy bilaterally. The definitive histological examination showed metastases in five of the ten nodes of the sixth level (pT1N1Mx) and latero-cervical lymph nodes free of disease. Later the patient was subjected to radioiodine therapy, and now she is free from disease. Her sister underwent echo-thyroid screening that showed multinodular goiter, with a suspicious lump of 2 cm in diameter, with a vascular pattern type IV and grade III FNA, located on the middle third of the right lobe, cervical-lymphadenopathy was absent, metastasis was suspected, and therefore was subjected to surgical treatment. During surgery, the piece was sent for histological examination of frozen sections of the suspected lump that diagnosed the presence of papillary thyroid carcinoma (pT1N0Mx) and for this reason we proceeded to the dissection of level VI laterocervical. Screening was extended to other family members and three third-degree relatives were diagnosed with multinodular goiter. They met both major criteria and one minor was diagnosed with FNMTC.

Case 2

A 54 year old man, a family history of benign thyroid diseases, was treated in our out-patients department for two years for thyroid nodule of 0.8 cm. The lump was hypoechoic, with type I vascular pattern, the patient had normal thyroid function, so he was subjected to therapy with levothyroxine and follow-up clinical, laboratory and ultrasound every six months. The last ultrasound showed the presence of a second suspicious lump of 1 cm echogenic upper pole of the left lobe with type III vascular pattern, was subjected to FNA (IIIB), so it signaled indication for surgery. During the surgery (thyrodectomy en bloc) the histological examination of frozen sections diagnosed of papillary thyroid cancer was performed. For that reason we continued with the dissection of level VI (pT1N1aM0). The sister 28 years old, treated for Hashimoto's thyroiditis during a routine ultrasound scan revealed the presence of a nodule of 1.2 cm at the inferior pole of the left lobe. The lump was echogenic, type III vascular pattern, FNA grade III, that the definitive histological examination after surgery diagnosed as papillary thyroid cancer. Also papillary thyroid microcarcinoma at

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the lower pole of the right lobe (pT (m) 1N0Mx) was diagnosed. Also in this case (presence of 1 major criterion and three minor) FNMTC, was diagnosed.

Discussion

About 95% of non-medullary thyroid tumors arise from follicular cells and about 3.5 to 6.2% of this fall within the group of non-medullary thyroid cancer families (Familial non-medullary thyroid cancer FNMTC). By FNMTC all thyroid tumors associated with other neoplastic syndromes (for example the S. Cowden, FAP) are excluded.

As for sporadic thyroid tumors, in FNMTC the histotype most frequent is the papillary tumor (> 90%) [1-2] and 36-57% cases of FNMTC occurs in a gland already affected by other pathological thyroid conditions (adenomatous goiter, Hashimoto's thyroiditis, hypothyroidism or hyperthyroidism) [1-2]. There are no microscopic differences that distinguish the FNMTC from sporadic tumors, even if the FNMTC may submit a trabecular structure with TCO cells (thyroid cell oxiphila). At the home of a suspected FNMTC is an autosomal dominant trait with incomplete penetrance, although it is not possible to exclude a polygenic trait [3]. Even up until today it has not been possible to determine, with certainty, which mutated genes can be correlated with FNMTC. There are many loci implicated: MNG1, TCO, fPTC / PRN and NMC1 [4], but in literature there isn't any corresponding data that identifies the association of mutation of this loci with FNMTC. The strong association between goitre and papillary thyroid cancer even in cases without familiarity, tends to assume that the multinodular goitre associated with papillary thyroid cancer is not only a familial syndrome. Probably in multinodular goiter there is a transformation of epithelial cell in thyroid cancer [3]. On the other hand it is equally common to see patients over the age of 60 diagnosed with a long history of nodular thyroid disease who do not develop thyroid cancer. This can be explained by incomplete penetrance of the autosomal dominant trait, hypothesis supported by genealogical analysis performed on different family groups [4]. Same factors have been identified for inclusion and exclusion FNMTC to identify families at risk of developing thyroid cancer (Table 1): Primary inclusion criteria are: 1) thyroid cancer in two or more first degree relatives, 2) multinodular goiter in three or more first or second degree relatives. Secondary inclusion criteria are: 1) early thyroid cancer, 2) multifocal and / or bilateral tumor, 3) tumor invasion of thyroid surrounding tissue, 4) benign thyroid disease in young patients of FNMTC family. There is hereditary predisposition to FNMTC if two primary criteria are satisfied or one primary criteria and three secondary criteria are satisfied.

Preconditions	-Exclusion of previus radiation exposure -Exclusion of neoplasia syndromes associated with PTC (e.g., accumulation of colorectal, ovarian, or breast carcinoma in the kindred) -Exclusion of somatic genetic alterations in the tumor DNA (e.g., RET/PTC rearrangements)
Primary criteria	- PTC in two or more first-degree blood relatives -Multinodular goiter in at least three first-degree or second-degree relatives of a PTC patient
Secondary criteria	-Diagnosis of PTC in patients younger than 33 years -Multifocal or bilateral PTC -Organ exceeding tumor growth (pT4) -Lymph node metastases (pN1) or distant metastases (M1) -Familial accumulation of adolescent-onset thyroid disease
Hereditary predisposition to PTC is considered in the following is/are present	-Two primary criteria or -One primary criteria plus three secondary criteria

Table 1: predictive criteria for identification of familial PTC/MNG families[3].

Exclusion criteria are: 1) exposure to radiation, 2) presence of neoplastic syndromes. When within a family there are two relatives with thyroid cancer the risk that members of the same family can develop thyroid cancer is between 31% and 53% [5,6], and if there are three relatives with thyroid cancer the risk increases to over 95% [5,6].

The main distinguishing characteristic of FNMTC in comparison to sporadic tumors is more aggressive [8]. The multicenter study conducted by Alsanea et al. [8] observed that 48 patients with FNMTC have a 44% incidence of relapse compared to 7% of sporadic tumors in the lowest disease-free survivor. Other distinctive features associated with the aggressiveness of the tumor are: 1) multifocality (71% -93% vs 19%) [9-11], 2) bilaterality (43% vs 8%) [9-11], 3) early lymph node invasion (57% vs 28%) [10,11], 4) early vascular invasion (43% vs 5%) [10,11].

With diagnosed FNMTC it woud be advised to put the patient's relatives in regular screening.

Ultrasonography is the best diagnostic tool for FNMTC because they are multifocal and bilateral. Uchino et al. [12] found a prevalence of 52% of thyroid nodules in asymptomatic relatives of patients with FNMTC, and 10% of these were diagnosed with thyroid cancer. Unlike ultrasound, the FNA did not demonstrate high accuracy and precision because FNMTC often are multifocal and bilateral and FNA has a false negative rate of 12% [13].

The early presentation and highly aggressive FNMTC justifies early screening, ten years earlier than the general population. In patients relatives with FNMTC who have diagnosed nodular thyroid disease Sipple et al. propose total thyroidectomy based on four factors: 1) the somatic mutation is present in all thyroid follicular cells, 2) the multifocality and bilaterality of cancer, 3) increased likelihood of metabolic treatment with I131 Radio, 4) allows the use of thyroglobulin in the follow-up post-operatively [14,15]. In FNMTC, regardless of the size, the strategy should be aggressive: total thyroidectomy with VI level-lymphadenectomy, followed by radioiodine therapy with I-131 and therapy with levothyroxine, maintaining TSH level at <0.1 mIU/l in patients at moderate risk, and TSH level at <0.05 in patients at high risk.

Conclusions

Currently the category of FNMTC is defined by very specific criteria that help to identify families whose members are exposed to the risk of developing FNMTC. All those who are susceptible to FNMTC should undergo clinical and ultrasound follow-up to detect early malignant lesions of the thyroid. In subjects at risk for FNMTC with suspicious nodules surgery is advised and in the case of pre-operative, intra-or postoperative diagnosis of PTC it is correct to adopt an aggressive treatment (total thyroidectomy + VI level lymphadenectomy followed by radioiodine therapy and hormone suppression therapy) in order to counter the aggressive behavior of FNMTC. Those small families with strong evidence for susceptibility to goitre / papillary thyroid cancer should also be included in FNMTC even though they don't fall within the criteria for inclusion in FNMTC.

References

1. Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, et al. (2001) 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 86: 5307-5312.
2. Grossman RF, Tu SH, Duh QY, Siperstein AE, Novosolov F, et al. (1995) Familial nonmedullary thyroid cancer. An emerging entity that warrants aggressive treatment. Arch Surg 130: 892-897.
3. Musholt TJ, Musholt PB, Petrich T, Oetting G, Knapp WH, et al. (2000) Familial papillary thyroid carcinoma: genetics, criteria for diagnosis, clinical features, and surgical treatment. World J Surg 24: 1409-1417.
4. Sippel RS, Caron NR, Clark OH (2007) An evidence-based approach to familial nonmedullary thyroid cancer: screening, clinical management, and follow-up. World J Surg 31: 924-933.
5. Burgess JR, Duffield A, Wilkinson SJ, Ware R, Greenaway TM, et al. (1997) Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. J Clin Endocrinol Metab 82: 345-348.
6. Charkes ND (2006) On the prevalence of familial nonmedullary thyroid cancer in multiply affected kindreds. Thyroid 16: 181-186.
7. Charkes ND (1998) On the prevalence of familial nonmedullary thyroid cancer. Thyroid 8: 857-858.
8. Alsanea O, Wada N, Ain K, Wong M, Taylor K, et al. (2000) Is familial non-medullary thyroid carcinoma more aggressive than sporadic thyroid cancer? A multicenter series. Surgery 128: 1043-1050.
9. Lupoli G, Vitale G, Caraglia M, Fittipaldi MR, Abbruzzese A, et al. (1999) Familial papillary thyroid microcarcinoma: a new clinical entity. Lancet 353: 637-639.
10. Mazzaferri EL (1987) Papillary thyroid carcinoma: factors influencing prognosis and current therapy. Semin Oncol 14: 315-332.
11. Hay ID (1990) Papillary thyroid carcinoma. Endocrinol Metab Clin North Am 19: 545-576.
12. Uchino S, Noguchi S, Yamashita H, Murakami T, Watanabe S, et al. (2004) Detection of asymptomatic differentiated thyroid carcinoma by neck ultrasonographic screening for familial nonmedullary thyroid carcinoma. World J Surg 28: 1099-1102.
13. Vriens MR, Sabanci U, Epstein HD, Ngai S, Duh QY, et al. (1999) Reliability of fine-needle aspiration in patients with familial nonmedullary thyroid cancer. Thyroid 9: 1011-1016.
14. Alsanea O, Clark OH (2001) Familial thyroid cancer. Curr Opin Oncol 13: 44-51.
15. Triponez F, Wong M, Sturgeon C, Caron N, Ginzinger DG, et al. (2006) Does familial non-medullary thyroid cancer adversely affect survival? World J Surg 30: 787-793.