

Familial Medullary Thyroid Carcinoma without MEN Syndrome: A Case Series Study

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Abstract

Medullary thyroid carcinoma (MTC) is the third most prevalent thyroid cancer and the most invasive form. This malignancy could be presented either in a sporadically or a familial pattern. Although the majority of cases with this disease are presented sporadically, familial screening is of great necessity in every MTC case since of all heritable cancers, MTCs are the most common malignancies. Therefore, after the familial screening of MTC patients using clinical symptoms along with paraclinical tools, the present study identified 19 familial medullary thyroid carcinoma (FMTC) cases in one family. Since most FMTCs are associated with multiple endocrine neoplasia's (MEN's) syndrome, it has attracted a great deal of scientific attention. This syndrome was ruled out herein through both genetic and clinical testing in these individuals. Thus, due to the scarcity of the familial form of this disease, the significant number of MTC in a family, and the absence of MEN syndrome in these people, we decided to report 19 patients with MTC in the same family without MEN's syndrome from southwest of Iran; this report emphasizes the necessity of familial screening even in the absence of the MEN's syndrome.

Keywords: Familial medullary thyroid carcinoma, Multiple endocrine neoplasia, Therapeutics

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Introduction

The prevalence of thyroid cancer is rising to the point where it is set to become the fourth most prevalent cancer in the world.¹ This increase in its global prevalence is attributed to various factors, including the development of the power to

diagnose the disease, individual risk factors (such as obesity), as well as certain factors, like increased exposure to environmental risk factors (such as iodine).² One of the thyroid cancers is papillary thyroid carcinoma. This cancer, which is also the most common type of thyroid

cancer, is known as a cancer with a good prognosis, despite the possibility of recurrence, metastasis, and cancer death of up to 15%.³ Follicular thyroid carcinomas (FTCs) are the second most common malignancies of all thyroid cancers. This cancer also has a relatively favorable prognosis. However, the absence of metastasis and optimal response to radioiodine therapy play a vital role in a good prognosis.^{4, 5} Finally, medullary thyroid carcinoma (MTC) is a rare malignancy of the thyroid gland, which originates from para-follicular C cells. This malignancy, accounting for only about 1 to 2% of thyroid cancers, is highly invasive and often metastasizes to the lymph nodes (including cervical and mediastinal), lungs, liver, and bone.^{6, 7} Only about a quarter of MTCs are familial, most of which present as part of multiple endocrine neoplasia (MEN) syndromes.⁸ Even though the majority of cases are not familial, it is recommended to perform familial screening in all MTC cases since among all heritable cancers, MTCs are the most common carcinomas. FMTC and MEN syndromes (including MEN2A and MEN2B) are familial syndromes with an incidence rate of 1 in 30000 individuals.⁹ Para -follicular or C-cells that produce calcitonin are the main cause of developing MTC.¹⁰ Histologically, MTC is characterized by neoplastic thyroid cells with polygonal to oval shaped nuclei, which are arranged in a trabecular or solid nests pattern with amyloid deposited stroma. The neoplastic cells have a positive reactive pattern for chromogranin A, synaptophysin, neuron specific

enolase (NSE), and calcitonin.¹¹ Pathologists believe that the pathognomonic finding for MTC is the amyloid deposition.¹² Therefore, in this article, we reported a family that included 19 patients of MTC without MEN's syndrome.

Case Presentation

In September 2018, a 51-year-old man came to our surgery clinic with a complaint of neck mass without any other problems, such as difficulty swallowing, hoarseness, or shortness of breath. The patient did not mention any serious past medical history. His physical examination revealed a mass with a size of approximately 3 × 5 cm in the left thyroid lobe and also another mass with an approximate size of 2 × 2 cm near the right lobe of thyroid. Ultrasound and laboratory tests reported hypo- and hetero-echoic masses with different diameters in the left and right lobes of the thyroid gland as well as a calcitonin level of 8500 pg/mL. The patient underwent surgery and the pathologist reported MTC, which was also confirmed by the immunohistochemistry (IHC). In less than 3 years, 2 other members of this family went to the surgical clinic with a similar complaint, and after going through the diagnostic process, their diagnosis of MTC was confirmed (Table 1/ cases number 2 and 3). Due to the important role of familial screening in early diagnosis of this malignancy and subsequent increase in survival, as recommended in Mohammed Mustafa's article, the rest of the family were screened via ultrasound imaging as well as blood calcitonin level and a total number

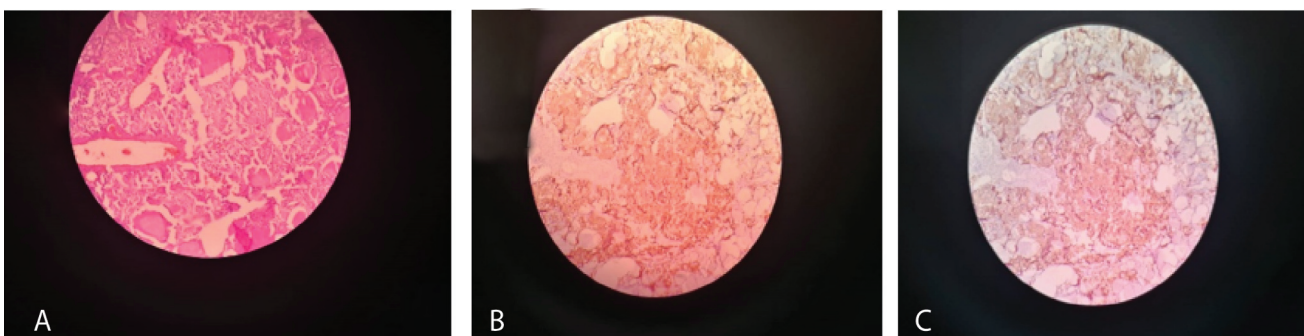


Figure 1. This figure shows histopathological features of the FMTC patients; A: Medullary thyroid carcinoma (H&E staining, × 20); B: Medullary thyroid carcinoma (Synaptophysin. IHC staining, × 20); C: Medullary thyroid carcinoma (Chromogranin A. IHC staining, × 20).

FMTC: Familial medullary thyroid carcinoma; H&E: Hematoxylin and eosin; IHC: Immunohistochemistry

of 19 MTC cases were found.¹³ Additionally, since most cases of MTC, especially in children, are associated with MEN syndrome, this syndrome was ruled out in this family according to clinical symptoms. It was also rearranged during transfection (RET) gene mutation.¹⁴ We had 19 cases of MTC in this family. All these cases were either siblings or uncle/aunt and nieces and nephews. Moreover, most of the marriages of this family were consanguineous. The patients were from 16 to 65 years of age. Among all these cases, none was related to MEN and we ruled out this syndrome clinically, which makes this case series very rare. Furthermore, all the patients were evaluated by an endocrinologist in terms of hyperparathyroidism and pheochromocytoma. After performing the relevant tests, no positive cases were found. The diagnosis of the patients was carried out based on history, physical examination, sonography, pathology, RET gene mutation, and blood calcitonin levels which were higher than the normal range (120 pg/mL to 8500 pg/mL) for all our cases. Carcinoembryonic antigen (CEA) was also measured for all the patients and the results ranged from 17.3 ng/mL to 33.1 ng/mL. All the subjects had the same histopathological figures (Figure 1). In the past medical history of our patients, we observed diabetes mellitus type 1 (two patients, cases number 11 and 15), varicocele (two patients, cases number 12 and 17), and testicular cancer (one patient, case number 6) and they did not have any past surgical history. Except for two cases that needed surgery four times (cases number 1 and 3), there was no need for any further surgeries for the rest of them. Total thyroidectomy and central neck lymphadenectomy were performed for all the cases. Furthermore, because of lymph node involvement, three of them needed unilateral lateral lymph node dissection (cases number 1, 9, and 17) and for one of them, bilateral lateral lymph node dissection was done (case number 2). None of our patients underwent chemotherapy or radiotherapy. In post-operation evaluations of our patients, there were no serious complications, such as infection and rebleeding; meanwhile, two subjects had hoarseness of voice that got better

after a few months (cases number 13 and 18). Two of our patients also experienced temporary hypocalcemia (cases number 1 and 3). In the paraclinic post-operation evaluation, all of our patients experienced a significant reduction in their blood calcitonin level (the post-operation range of blood calcitonin was from 6/16 pg/ml to 49/3 pg/ml). Ultimately, in the follow-up of our patients to date, all of them are fortunately alive and there are only two cases that have experienced tumor recurrence (Table 1).

It should be noted that patients were assured that the secrets of them maintain in accordance with Helsinki Treaty at the beginning of this study. Furthermore, patients were not charged any additional fees. The ethics committee of Yazd Shahid Sadoughi University of Medical Sciences has approved the project with the code of IR.SSU.MEDICINE.REC.1401.002.

Discussion

MTC is known to be the third most prevalent thyroid carcinoma. It was first described in 1959. Familial and sporadic cases have been reported recently. Imaging could not differentiate them from other thyroid carcinoma, such as follicular carcinoma and papillary thyroid carcinoma.¹⁵ FNA from the mass could confirm the diagnosis. Although the histopathological study is a gold standard for diagnosis of MTC, patients' clinical symptoms such as diarrhea and flushing caused by calcitonin secretion are also helpful.¹⁶ Neoplastic cells could metastasize via lymphatic channels and involve the cervical lymph nodes, in addition to mediastinal lymph nodes and other tissues, such as the liver, bone, and lungs. The neoplastic cells secrete both calcitonin and CEA; thus, the measurement of these serum markers is conducive to the diagnosis of this type of thyroid neoplasm.⁷ As Graves indicated, the majority of MTC cases in children are inheritable and accompanied by MEN syndromes. Moreover, researchers in this article, despite advice about screening and treatment of MTC, recommended prophylactic surgery for whom we diagnosed in genetic screening.¹⁴ Mohammed Mustafa also considered this malignancy as a poor prognosis

Table 1. Demographic information and preoperative studies of the MTC patients (continued)

Order of admission	Age	Sex	Chief complaint	Imaging	CEA level	Preoperation blood calcitonin level	Post-operation blood calcitonin level	RET gene mutation
1	51	Male	Thyromegaly	Right lobe of thyroid: a 26 × 15 mm hypoechoic mass; Left lobe of thyroid: a 58 × 28 × 43 mm heteroechoic mass and a 25 × 15 mm mass at the posterior part of the left SCM muscle	33.1 ng/mL	8500 pg/mL	20.62 pg/mL	Negative
2	55	Male	Thyromegaly	Right lobe of thyroid: a 19 × 30 mm hypoechoic mass; Left lobe of thyroid: a 25 × 32 mm hypoechoic mass	26.2 ng/ml	2200 pg/mL	49.3 pg/mL	Negative
3	41	Female	Thyromegaly	Right lobe of thyroid: a 20 × 34 mm heteroechoic mass Left lobe of thyroid: a 22 × 24 mm hypoechoic mass	25.5 ng/mL	1100 pg/mL	15.4 pg/mL	Negative
4	65	Female	Screening	Right lobe of thyroid: a 8.5 × 4.8 mm hypoechoic nodule; Left lobe of thyroid: a 2.1 × 7.5 mm isoechoic nodule	19.1 ng/mL	340 pg/mL	7.97 pg/mL	Negative
5	16	Male	Screening	Right lobe of thyroid: a 8.2 × 3.6 mm hypoechoic nodule; Left lobe of thyroid: a 2.7 × 4.2 mm hypoechoic nodule and a 10 × 10 mm isoechoic nodule	24.2 ng/mL	120 pg/mL	7.23 pg/mL	Negative
6	31	Male	Screening	Right lobe of thyroid: some isoechoic nodule with the largest size of 30 × 21 mm Left lobe of thyroid: a 26 × 10 mm hypoechoic nodule	22.9 ng/mL	840 pg/mL	8.31 pg/mL	Negative
7	38	Female	Screening	Right lobe of thyroid: a 2.7 × 2.2 mm hypoechoic nodule Left lobe of thyroid: a 1.9 × 1.7 mm hypoechoic nodule	20.8 ng/mL	270 pg/mL	6.47 pg/mL	Negative
8	25	Male	Screening	Right lobe of thyroid: a 8.7 × 3.2 mm hypoechoic nodule; Left lobe of thyroid: a 4.1 × 5.8 mm isoechoic nodule	18.7 ng/mL	350 pg/mL	8.41 pg/mL	Negative
9	46	Female	Screening	Right lobe of thyroid: a 15 × 18 mm hypoechoic nodule and a 1.9 × 2.7 mm isoechoic nodule Left lobe of thyroid: a 25 × 28 mm hypoechoic nodule	19.3 ng/mL	690 pg/mL	9.38 pg/mL	Negative
10	23	Male	Screening	Right lobe of thyroid: a 15 × 24 mm hypoechoic nodule; Left lobe of thyroid: a 25 × 32 mm hypoechoic nodule	25.6 ng/mL	750 pg/mL	7.85 pg/mL	Negative
11	36	Female	Screening	Right lobe of thyroid: a 7.1 × 6.3 mm hypoechoic nodule; Left lobe of thyroid: a 9 × 17 mm hypoechoic nodule	27.1 ng/mL	450 pg/mL	6.79 pg/mL	Negative
12	39	Male	Screening	Right lobe of thyroid: a 13 × 22 mm hypoechoic nodule; Left lobe of thyroid: a 25 × 17 mm hypoechoic nodule	23.6 ng/mL	670 pg/mL	6.94 pg/mL	Negative
13	48	Female	Screening	Right lobe of thyroid: a 9.5 × 11.4 mm isoechoic nodule; Left lobe of thyroid: a 8.3 × 5.1 mm hypoechoic nodule	19.8 ng/mL	490 pg/mL	6.16 pg/mL	Negative
14	29	Male	Screening	Right lobe of thyroid: a 6.7 × 8.2 mm hypoechoic nodule; Left lobe of thyroid: a 3.1 × 1.2 mm hypoechoic nodule and a 4.3 × 2.2 mm hypoechoic nodule	17.7 ng/mL	180 pg/mL	7.64 pg/mL	Negative
15	33	Female	Screening	Right lobe of thyroid: a 19.6 × 12 mm hypoechoic nodule; Left lobe of thyroid: a 11.7 × 9.3 mm hypoechoic nodule	22.7 ng/mL	650 pg/mL	9.52 pg/mL	Negative
16	30	Male	Screening	Right lobe of thyroid: a 8.4 × 7.4 mm hypoechoic nodule; Left lobe of thyroid: a 11.2 × 10.2 mm hypoechoic nodule	21.4 ng/mL	570 pg/mL	9.13 pg/mL	Negative
17	42	Male	Screening	Right lobe of thyroid: a 8.5 × 10.5 mm hypoechoic nodule; Left lobe of thyroid: a 6.7 × 5.2 mm isoechoic nodule	25.9 ng/mL	460 pg/mL	7.42 pg/mL	Negative

Table 1. Demographic information and preoperative studies of the MTC patients (continued)

Order of admission	Age	Sex	Chief complaint	Imaging	CEA level	Preoperation blood calcitonin level	Post-operation blood calcitonin level	RET gene mutation
18	49	Male	Screening	Right lobe of thyroid: a 9.5 mm hypoechoic and a 8 mm isoechoic nodule; Left lobe of thyroid: four hypoechoic nodule with the largest size of 12 mm, and a 9 × 8 mm isoechoic nodule	17.6 ng/mL	230 pg/mL	6.26 pg/mL	Negative
19	54	Female	Screening	Right lobe of thyroid: a 4.4 × 3.1 mm hypoechoic nodule; Left lobe of thyroid: a 2.9 × 5.6 mm hypoechoic nodule	18.3 ng/mL	130 pg/mL	8.35 pg/mL	Negative

MTC: Medullary thyroid carcinoma; RET gene: Rearranged during Transfection gene; CEA: Carcinoembryonic antigen; SCM: Sternocleidomastoid

carcinoma with 13% of mortality among all thyroid cancers. This shows the importance of early diagnosis, specifically in familial screenings, to achieve an increase in survival of the patients.¹³ Tricia A. Moo-Young reported that the majority of MTC cases are sporadic. Nonetheless, given the fact that among all inheritable cancers, MTC is the most familial one, the familial screening in this setting is of particular importance.⁹ Marybeth S. Hughes also defined MEN syndromes as rare endocrine syndromes that are characterized by tumors of c-cell of the thyroid, adrenal, and parathyroid. He also defined FMTC as a variant of MEN 2A; as we mentioned previously, FMTC without MEN syndrome is a very rare condition.¹⁷ SA Wells Jr, in his article, emphasized that RET gene mutation screening is the most certain way for diagnosing MEN syndromes and also mentioned that managing this disease requires a good level of understanding concerning its different behaviors and variable presentations, especially according to specific RET gene mutation.¹⁸

Another work was also conducted by Donato Iacovazzo et al. on RET negative FMTCs in four families around the world. In contrast to the current report, in terms of number, except for one family with 11 cases, in other families, five or less than five people were affected by the disease. Another point is that in this study, genetic testing was performed for all the individuals, while in the above-mentioned paper, genetic testing was performed only for the affected members of the family.⁸

There are several remarkable things in this case series. Initially, as mentioned before, although

FMTCs are less common than MTC cases, we presented FMTC cases that were not related to MEN syndrome, which makes this presentation so rare. On the other hand, we talked about 19 patients, which is a very large number of FMTC cases that can occur in a family group. This reveals the importance of familial screening in medullary thyroid carcinoma.⁹ Additionally, as we reported previously, in post-operation evaluations of our patients, in addition to the absence of any serious complications, such infection or rebleeding, only two had hoarseness of voice that got better after a few months (cases number 13 and 18), and two experienced temporary hypocalcemia that was not a major complication (cases number 1 and 3). The blood calcitonin level of all the cases showed a significant decrease following the operation (the pre-operation range was 120 pg/ml to 2200 pg/ml and the range of blood calcitonin post-operation was 3/49 pg/ml to 16/6 pg/ml).

Although there are physiological or pathological conditions that can increase serum calcitonin levels including; proton pump inhibitors, β -blockers, and glucocorticoids; Hashimoto's thyroiditis; renal insufficiency; follicular and papillary thyroid carcinomas; C-cell hyperplasia, and neuroendocrine; nevertheless, there was a significant relationship between the size of the thyroid nodules, their aggressiveness, and the level of calcitonin in FMTC cases.¹⁹⁻²¹

Not only should physicians consider false positives for calcitonin levels, but also delays or failure in diagnosis, performing curative treatment for FMTC cases, and the negative effect of this issue on the prognosis of these patients should be considered (Table 1).²²

Conclusion

As discussed earlier, MTC is the third most common form of thyroid cancer. As evaluated in this research, although the familial form of MTC is much less common than its sporadic form, in dealing with an MTC case, apart from the relevant standard management, the necessity of familial screening must be considered. It is also noteworthy that FMTCs have the ability to occur without MEN's syndrome and without mutation in the RET gene.

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Informed Consent

Informed consent was obtained from all the participants in this study.

Conflict of Interest

None declared.

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