

Surgical and clinical strategies in the management of thyroid medullary carcinoma in children with and without ret proto-oncogene mutations

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Medullary thyroid carcinoma (MTC) may arise sporadically or in familial manner. We presented sporadic and familial cases with MTC in order to raise awareness on management of such patients. Three medullary thyroid carcinoma (MTC) cases were presented. Case 1 had RET634 mutation; managed with total thyroidectomy (TT) and cervical lymph node dissection (CLND). Case 2 had RET804 mutation; managed with prophylactic TT. Case 3 had thyroid nodule; managed with TT and CLND. Case 1 had micro-carcinomatosis foci, Case 2 had normal thyroid tissue in histopathological examination and Case 3 had medullary thyroid carcinoma with tumor negative surgical borders. Case 1 was re-operated for persisting focus of disease. Follow-up of cases were uneventful. Clinicians and surgeons should be aware of critical timing for surgery and various surgical and clinical strategies in the management of MTC in children.

Key words: medullary thyroid carcinoma, multiple endocrine neoplasia, surgery, RET proto-oncogene.

Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine tumor originated from calcitonin-secreting parafollicular or C cells of the thyroid^{1,2}. MTC arises not only sporadically but also in a hereditary manner associated with multiple endocrine neoplasia type 2 (MEN2) syndromes and familial medullary thyroid carcinoma (FMTC). MEN 2A is characterized by MTC, pheochromocytoma and primary hyperparathyroidism, whereas MEN 2B is characterized by MTC, pheochromocytoma and mucosal ganglioneuromas³. While the risk of developing MTC in MEN 2A is 90-100%, the risk of developing pheochromocytoma and hyperparathyroidism is 50% and 20-30% respectively¹. Various variant forms such as MEN2A+Hirschsprung disease, MEN2A+cutaneous lichen amyloidosis are also described in association with MEN2A. On the other hand, MTC is present in 100% of the

cases with MEN2B and marfanoid habitus is present in 100% and pheochromocytoma and mucosal ganglioneuroma accompany those in 50% each³.

Since the relationship between RET proto-oncogene mutation and MTC, especially familial one, is well-known, the DNA analysis has become an essential routine investigation in patients with MTC. The aggressiveness of MTC varies according to the mutated codon of RET proto-oncogene. Therefore, the patients are classified into different risk groups and managed accordingly⁴. The American Thyroid Association (ATA) established current management recommendations with the aim of preventing MTC before it becomes an aggressive metastatic disease⁴. On the other hand, it is also important to minimize the surgical risks of total thyroidectomy (TT). Therefore, timing of prophylactic TT has also

been defined according to the risk groups of RET mutations in MEN⁴. Sporadic MTCs are generally seen after 20 years of age and recommended to be managed with TT before development of metastasis to other organs¹.

Herein, we presented three cases; two of which had previously known RET proto-oncogene mutations of different codons and the other had no known mutation in order to raise awareness on surgical and clinical management of such patients.

Case Reports

Case 1

A 6-year-old boy was referred to our hospital with a strong family history of MTC. His father, his paternal uncle, his grandfather and his two cousins were diagnosed with MTC. Medical history of the patient did not show evidence of Hirschsprung's disease. The genetic testing of the patient revealed heterozygosity of codon 634 mutation (C634Y). The preoperative laboratory examinations revealed that the patient was euthyroid under 25 µg/day levothyroxine treatment. The serum calcitonin level was elevated (149 pg/ml, N: 0-18). The parathyroid hormone level (PTH) was 18.6 pg/ml (N: 12-88), serum total calcium level was 10.1 mg/dl (N: 8.4-10.2), ionized calcium was 1.2 mmol/dl (N: 1.23-1.38), serum phosphorus level was 5.4 mg/dl (N: 2.7-4.9), and alkaline phosphatase was 154 U/L (N: <390). The 24-hour urine analysis of metanephrine and normetanephrine values were 74 µg/d (N: 52-341) and 89 µg/d (N: 88-444) respectively. The thyroid ultrasound (US) revealed normal findings except bilateral jugular and cervical lymphadenopathies. The parathyroid scintigraphy revealed normal findings. The whole body examination with sestamibi scintigraphy revealed bilateral jugular and cervical lymph nodes involvement (Fig. 1). Abdominal US was normal.

The intraoperative exploration revealed that thyroid gland was normal macroscopically. TT was performed and bilateral recurrent laryngeal nerves and parathyroid glands were preserved. Central compartment and bilateral lateral-cervical lymph node dissection (modified neck lymph node dissection) was performed. His postoperative follow-up was uneventful and he was discharged on 3rd postoperative

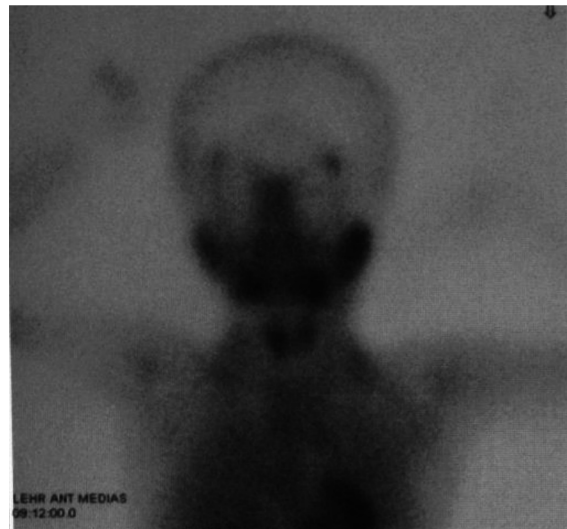


Fig. 1. The sestamibi scintigraphy of Case 1 revealing bilateral jugular and cervical lymph node involvement; the black dotted areas revealing positive involvement of bilateral jugular and cervical lymph nodes.

day. The histopathological examination revealed 3 foci of thyroid medullary micro-carcinoma and metastasis in five of lymph nodes located next to thyroid gland. The tumor cells of micro-carcinoma foci were positively stained with chromogranine, CD56 and calcitonin; and negatively stained with thyroglobulin (Tg) (Fig. 2). Postoperative calcitonin level was 28.1 pg/ml (N: 0-18) and Tg level was 4.25 ng/ml (N: 0.15-50). Calcitonin levels increased gradually to 43.1 pg/ml and ultrasound revealed a suspected residual tissue of 4x8 mm. Therefore, re-exploration was performed after labeling of the focus with ¹³¹Iodine injection and the focus was excised with the aid of gamma probe guidance during operation. The histopathological examination revealed MTC metastasis in the excised lymph node. The patient is still under follow-up uneventfully.

Case 2

A 13-year-old boy was referred to our hospital with a strong family history of MTC. His father, his paternal uncle, his 4 paternal aunts, three siblings were diagnosed with MTC. Medical history of the patient did not show evidence of Hirschsprung's disease. Upon physical examination, he had no goiter. No nodules were detected in the thyroid ultrasonography and thyroid dimensions were normal. The genetic testing of the patient revealed heterozygosity of codon 804 mutation (Exon 14 p. V804M

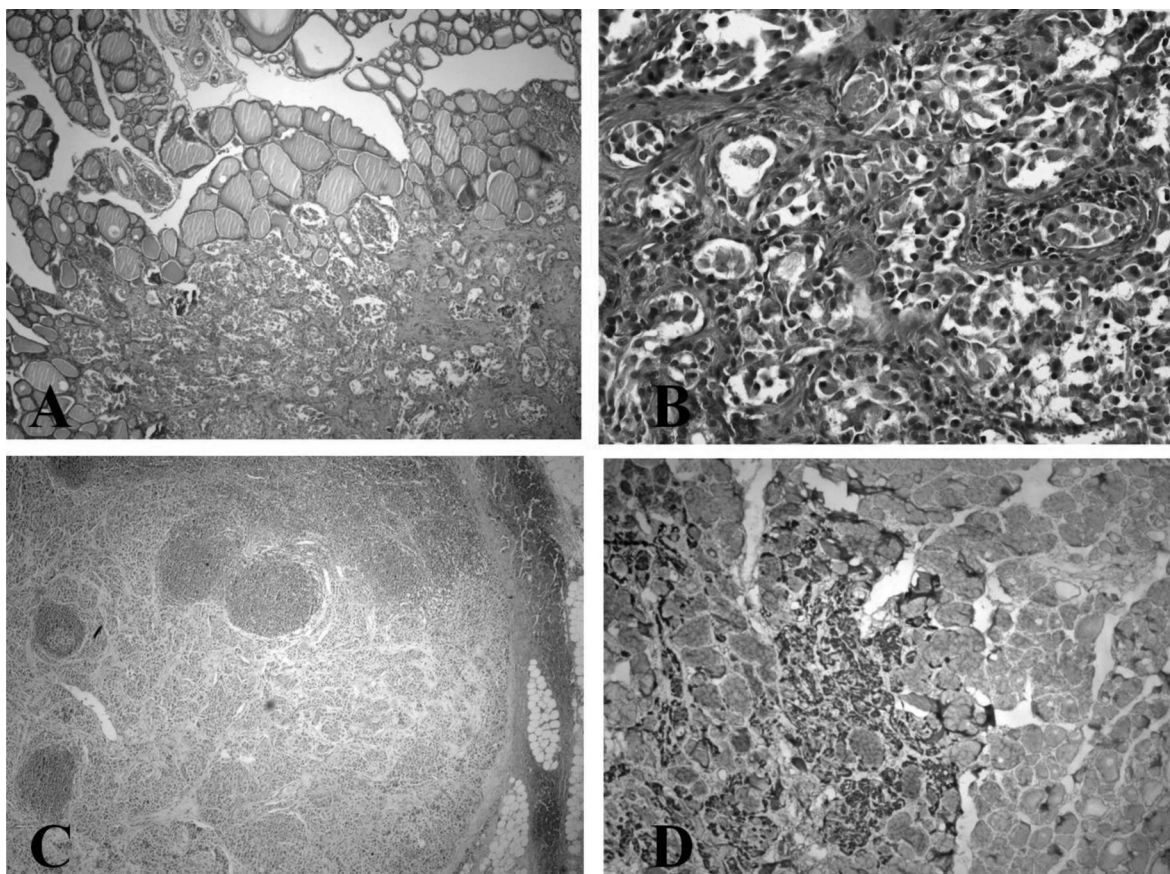


Fig. 2. Histopathologic examination of first case;

- 2A. Tumor with a diameter of 0.5 cm in thyroid tissue without a capsule (HE, X40).
- 2B. Tumor cells of thyroid medullary carcinoma shown in Fig 2A (HE, X200).
- 2C. Metastasis of thyroid medullary carcinoma to cervical lymph node (HE, X100).
- 2D. Calcitonin positivity of tumor cells of thyroid medullary carcinoma (immune-peroxidase, X40).

(c.G2410A)). The preoperative laboratory examinations revealed that the patient was euthyroid. The serum calcitonin level was normal (3.52 ng/L, N: 0-18). The parathyroid hormone level (PTH) was 72.9 pg/ml (N: 12-88), serum total calcium level was 9.9 mg/dl (N: 8.4-10.2), ionized calcium was 1.3 mmol/dl (N: 1.23-1.38), serum phosphorus level was 4.5 mg/dl (N: 2.7-4.9), and alkaline phosphatase was 304 U/L (N: <390). The 24-hour urine analysis of metanephrine and normetanephrine was within normal limits.

This case had single mutation in codon 804 and thus accepted to be in the lowest risk group for development of MTC. The cases in this risk group are recommended to have annual calcitonin and cervical US follow-up and to undergo prophylactic thyroidectomy no later than 10 years of age. Therefore, thyroidectomy was performed and bilateral

recurrent laryngeal nerve and parathyroid glands were preserved. The intraoperative exploration revealed that thyroid gland was normal macroscopically. His postoperative follow-up was uneventful and he was discharged on 3rd postoperative day. The histopathological examination revealed normal thyroid gland. The case is being followed-up on calcium and PTH tests for hyperparathyroidism and with metanephrine/ normetanephrine screening in 24-hour urine for pheochromocytoma.

Case 3

A 16-year-old boy was referred to our hospital with a palpable mass in his neck. He had no systemic symptoms such as: headaches, sweating, hot flashes, red flushed face, fatigue, weight loss, sense of palpitation, diarrhea, vomiting, or abdominal pain. His past medical history and family history were unremarkable.

There were no family members with a history of MTC. His blood pressure and pulse rate were within normal ranges and he had no mucosal neurinomas. The laboratory examinations revealed that the patient was euthyroid. The serum calcitonin level was >100 pg/ml (3.52 ng/L, N: 0-18), thyroglobulin was 39.6 ng/ml (N: 0-60), Carcinoembryonic antigen (CEA) was 9.2 ng/ml (normal level in healthy men: 0.37 – 3.3 ng/ml and < 6.2 ng/ml in cigarette smokers).

Ultrasonography revealed heterogeneous nodule measuring 28x34 mm with cystic and solid regions in the left thyroid and there was no pathological lymph nodes. Fine needle aspiration biopsy was performed and histopathological examination revealed medullary thyroid carcinoma. The preoperative evaluation of the patients who were diagnosed to have MTC with a fine needle aspiration biopsy should include a clinical and laboratory screening for pheochromocytoma and hyperparathyroidism in addition to calcitonin and CEA measurements⁴. Thyroid cancer can be the index case of the syndromes. Serum calcium level was 9.4 mg/dl (N: 8.5-10.2), phosphorus level was 4.6 mg/dl (N: 2.5-4.5), serum ALP was 155 IU/L (N: 52-171), and PTH level was 59.4 pg/ml (N: 10-65). The 24-hour urine catecholamine metabolites were normal. Additionally, for the same reason, all cases should be evaluated in terms of the RET proto-oncogene “germline” mutations even if no medullary cancer is present in the family history. No mutation was present in the RET proto-oncogene in this case.

Thyroidectomy and a central neck dissection were performed. Postoperative serum calcitonin level was < 2 ng/ml and the CEA level was 0.5 ng/ml. The case is still under follow-up with calcitonin measurement every six months for four years without any recurrence of the disease.

Discussion

Medullary thyroid carcinoma (MTC), encountered in children and adolescents, is generally thought to be the hereditary form secondary to a mutation in the RET proto-oncogene. The occurrence of medullary thyroid carcinoma in MEN2 and FMTC syndromes is almost certain and it may become metastatic

carcinoma even in the early stage of the disease^{1, 5, 6}. The presentation and prognosis of the disease depends on the type of mutation on RET proto-oncogene^{1, 6}. Therefore, genetic testing of all family members even before 5 years of age is crucial if there is a known family member. Case 1 and 2 were diagnosed by genetic testing because they have relatives diagnosed as MTC. Case 3 was a sporadic MTC without a known RET mutation.

Germline RET mutations are present in 25% of the cases, which are called hereditary MTC. Somatic (acquired) RET proto-oncogene mutations at exon 10, 11, 15, and 16 are present in 65% of cases with sporadic MTC^{7, 8}. Therefore, genetic screening for the germline RET oncogene is recommended in all cases. When an index case is found to be positive for a germline mutation, all other family members should be screened for this mutation and genetic counseling should be provided. The germline RET proto-oncogene mutation has been reported in 95% of cases with MEN2A and 2B and 88% of cases with FMTC, respectively^{9, 10}. When a germline RET mutation is found to be positive and thyroid examination is normal, calcitonin measurement should be performed starting six months of age in cases with MEN2B and at 3 years of age in cases with MEN2A and FMTC. Similarly, a detailed neck ultrasound examination should be performed immediately in all cases with MEN2B, and after 3-5 years of age in cases with MEN2A and FMTC⁴.

Prophylactic thyroidectomy should be planned according to the degree of risk of the mutation detected in the family members. It should be kept in mind that the most effective treatment of MTC is prevention before it develops by TT. However, timing of TT is the critical issue since there is a delicate balance between treatment of MTC and complications of TT. The American Thyroid Association guidelines defined four risk categories of MTC for timing of TT⁴. TT should be performed in risk level D (MEN 2B cases with mutations in codons 918, 883 and tandem mutations in codons 804-805, 804-806, 804-904) within first year of life; in risk level C (Mutations in codons 630 and 634) before 5 years of age preferably between 2-4 years of age; in risk level B (Mutations in codons 609, 611, 618, 620, 630 and tandem mutations in codons 804-778) before 6 years

of age; in risk level A (mutations in codons 533, 635, 649, 666, 768, 790, 791, 891, 912, and single mutation in codon 804) before 10 years of age^{1,4,11-19}.

In the literature, it was reported that prophylactic central lymph node dissection is not necessary in all cases^{1,4,6}. But, central neck lymph node dissection is advised to be performed if there is evidence of lymph node metastasis, elevated serum calcitonin level > 40 pg/ml, nodule dimension > 5 mm or in cases older than 1 year of age who are in the high risk group^{1,15,18,20,21}. Case 1 had codon 634 mutation and TT was performed when he was 6 years of age. In the present study, we performed lymph node dissection in Case 1 because there were palpable cervical lymph nodes, and ultrasound and scintigraphy revealed pathological lymph node involvement and serum calcitonin level was higher than 40 pg/ml (149 pg/ml). Case 2 had codon 804 mutation and TT was performed when he was 13 years of age. We did not perform central lymph node dissection in Case 2 since there were no pathological findings in preoperative laboratory and radiological examinations. Unfortunately, we operated the patients at an age later than the one recommended in ATA guidelines because they were admitted to our hospital late. According to the ATA guidelines, prophylactic TT may be delayed if there is no evidence of lymph node metastasis, basal calcitonin level is under 40 pg/ml, and thyroid nodules in ultrasound are smaller than 5 mm⁴. However, there are several reports against the delay criteria of ATA guidelines. Morris et al.² reported that US should not be used to determine timing of surgery since it is not reliable enough to show microscopic MTC. On the other hand, delaying surgical management more than recommended in guidelines is reported as the only predictor factor for persistence and recurrence of disease²²⁻²⁴.

Post-operatively, close follow-up is recommended in MTC patients for recurrence of MTC^{4,22-24}. The serum calcitonin level and CEA are the tumor markers used in the postoperative follow up of MTCs^{25,26}. Cases with a normal postoperative serum CEA and a low calcitonin level that cannot be measured are accepted as biochemically cured and have the best prognosis. According to the guidelines calcitonin levels

should be measured 2-3 months after the first operation²⁷. A cure is achieved when the basal calcitonin level is at an unmeasurable level and then, a routine calcitonin measurement should be performed in every six months for the first two to three years, followed by annual calcitonin measurements. A high calcitonin level in six months or more after the operation indicates residual disease. In the postoperative follow-up of Case 1 had gradually elevating calcitonin levels and underwent excision of residual focus. Recurrence usually occurs 5-7 years after the surgery; therefore patients should be followed for a long period^{1,28}. The follow-up period is 2 months in Case 1, 2 years in Case 2 and 4 years in Case 3 in the present study. Therefore, it might not be true to have a firm conclusion on the long-term results of these cases.

In addition post-operative follow-up is recommended for the other components of MEN syndromes. Since the risks of pheochromocytoma and hyperparathyroidism are high in carriers of codons 630 and 634 mutations, they should be annually followed-up by checking free metanephrine and normetanephrine in plasma or 24-hour urine catecholamine metabolites for pheochromocytoma and serum calcium and PTH measurement for hyperparathyroidism after 8 years of age and starting after 20 years in carriers of other mutations^{29,30}. Both Case 1 and Case 2 will be followed up for the components of MEN syndromes accordingly since their mutations carry the risk of developing these diseases.

Herein, we presented one sporadic MTC case and two late-admitted hereditary MTC cases; one of whom was managed by TT and cervical lymph node dissection and the other was managed by prophylactic TT. Long-term results are also needed to have a firm conclusion. By means of these cases, an approach to MTC in childhood and RET oncogene positivity was discussed. It was aimed to raise awareness on various management strategies in the treatment of MTC and critical timing for surgery which is important for better prognosis and survival.

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