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Medullary Thyroid Carcinoma: A Rare Diagnosis

Medüller Tiroid Karsinomu: Nadir Bir Tanı

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ABSTRACT

Objective: The aim of this study was to analyze the clinical, imaging, pathological and postoperative surveillance data of patients with medullary thyroid carcinoma (MTC).

Method: We included 11 patients who underwent surgery. The surgical type was documented. Clinical characteristics and imaging findings as well as preoperative and postoperative calcitonin and carcinoembryonic antigen (CEA) levels and preoperative thyroid stimulating hormone (TSH) levels were retrospectively reviewed. The demographic characteristics of the patients were also noted.

Results: The mean age of the patients was 53.7 ± 12.8 years, and the mean nodule size was 27 ± 18 (range, 9-70) mm. The mean preoperative TSH level was 1.1 ± 1.0 mIU/L, and the median calcitonin and CEA levels were 898 (range, 10.9-1747) pg/mL and 98.1 (range, 44-196) ng/mL, respectively. Total thyroidectomy and central/lateral lymph node dissection were performed in all patients. According to preoperative fine-needle aspiration biopsy results, two (18.2%) patients were classified as Bethesda 2 and one (9.1%) as Bethesda 4 and eight (72.7%) patients had MTC. Of the patients, seven (63.6%) were in the early stage and four (36.4%) were in the localized advance stage. One patient had ret proto-oncogene-positive hereditary MTC and 10 had sporadic MTC. During the follow-up, one (9.1%) patient died because of lung metastasis.

Conclusion: For the preoperative diagnosis of MTC, clinical characteristics, imaging findings, cytology test results, and genetic test results as well as serum calcitonin and CEA levels should be comprehensively evaluated. As a clinical approach, obtaining preoperative calcitonin and CEA levels for patients with thyroid nodules scheduled for thyroidectomy is advisable.

Keywords: Medullary thyroid carcinoma, calcitonin, carcinoembryonic antigen, thyroidectomy

ÖZ

Amaç: Bu çalışmanın amacı, medüller tiroid karsinomlu (MTK) hastalarının klinik, görüntüleme, patolojik ve postoperatif gözetim bulguları verilerini belgelemek ve analiz etmektir.

Yöntem: On bir hasta dahil edildi. Tüm hastalar ameliyat edildi ve cerrahi tipi belgelendi. Bu hastaların klinik özellikleri ve görüntüleme özellikleri, ameliyat öncesi ve sonrası kalsitonin ve karsinoembriyojenik antijen (CEA) düzeyleri ve ameliyat öncesi tiroid uyarıcı hormon (TSH) düzeyleri geriye dönük olarak gözden geçirildi. Hastaların demografik özellikleri listelendi.

Bulgular: Ortalama yaş 53,7 ± 12,8, ortalama nodül boyutu 27 ± 18 mm olarak belirlendi. Ortalama preoperatif TSH değeri 1,1 ± 1,0 mIU / L, ortanca kalsitonin ve CEA değerleri sırasıyla 898 (10,9-1747) pq/mL ve 98,1 (44-196) ng/mL idi. Tüm hastalara total tiroidektomi + santral/lateral lenf nodu diseksiyonu uygulandı. Preoperatif ince iğne aspirasyon biyopsisi (İİAB) sonuçlarına göre iki (%18,2) hasta Bethesda 2, bir (%9,1) Bethesda 4 ve 8 (%72,7) hasta MTK olarak rapor edildi. Hastalardan 7'si (%63,6) erken evrede, 4'ü (%36,4) lokalize ileri evrede idi. Bir hasta RET onkogen pozitif kalıtsal MTC olarak değerlendirildi ve 10 hasta sporadik MTK olarak değerlendirildi. Takip sırasında 1 (%9,1) hasta akciğer metastazı nedeniyle kaybedildi.

Sonuç: MTK'nin preoperatif tanısı için klinik ve görüntüleme bulguları, sitoloji ve serum kalsitonin ve CEA seviyeleri, genetik testler kapsamlı bir şekilde değerlendirilmelidir. Klinik bir yaklaşım olarak, tiroidektomi planlanan tiroid nodülü olan hastalarda ameliyat öncesi kalsitonin ve CEA ölçümü alınmalıdır.

Anahtar kelimeler: Medüller tiroid karsinomu, kalsitonin, karsinom biyometrik antijen, tiroidektomi

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INTRODUCTION

The incidence of thyroid cancer has increased in recent years. Medullary thyroid carcinoma (MTC) accounts for approximately 1-10% of all thyroid malignancies and 0.4-1.4% of all thyroid nodules. It has an incidence of 0.11 per 100,000 and is responsible for approximately 13% of all deaths due to thyroid cancer. Most MTC cases are sporadic, but up to 25% are associated with an inherited mutation in the ret proto-oncogene (RET) [1,2].

MTC is derived from parafollicular or calcitonin-producing C-cells (C-cells), which are of neuroendocrine origin and located in the thyroid gland. However, MTC exhibits more aggressive behaviors, such as local lymph node and distant metastases and recrudescence, than other types of differentiated thyroid carcinoma. Therefore, diagnosing MTC before surgery is important for patients and surgeons [1-3].

With the discovery of genetic tests that detect RET mutations, significant advances have been made in the diagnosis and treatment of MTC. These tests are recommended for anyone diagnosed with MTC. If a germline mutation is detected in a patient with MTC, relatives are screened to identify those with genetic predisposition, and these cases can be treated with prophylactic total thyroidectomy. In addition, tumor markers such as calcitonin and carcinoembryonic antigen (CEA) help in determining the extent of surgery and detecting recurrence earlier. Tyrosine kinase receptor inhibitors used in metastatic diseases have positive effects on both disease progression and disease-free survival. Guidelines created in recent years recommend bilateral central neck dissection together with total thyroidectomy for the treatment of MTC [3].

The aim of this study was to analyze the clinical, radiologic, pathological, and postoperative surveillance findings of patients with MTC in our clinic.

MATERIAL and METHODS

A total of 11 patients who underwent surgery at a tertiary training and research hospital between 2015 and 2019 were included in the study. Ethical approval was obtained from the hospital ethics committee. Pathology results were retrospectively analyzed from the hospital electronic record archive. The surgical type was documented. Clinical characteristics and imaging findings as well as preoperative and postoperative calcitonin and CEA levels and preoperative thyroid stimulating hormone levels were retrospectively reviewed. The demographic characteristics of the patients were also noted.

Statistical Analysis

The frequency and percentage were obtained for categorical variables, and median, mean, and standard deviation values were obtained for continuous variables. Normality test of continuous variables was performed using the Shapiro-Wilk test. Mean and standard deviation were obtained for normally distributed continuous variables and median values (interquartile range) for non-normally distributed variables. The Friedman test was used to compare dependent continuous variables that did not show normal distribution. The Wilcoxon test was used for in-group comparison of dependent continuous variables that did not show normal distribution. Bonferroni correction was used to calculate the P value. P values of < 0.005 were considered significant. All analyses were conducted using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

MTC was detected in 11 (1.2%) of 884 patients who underwent total thyroidectomy between 2015 and 2019. The mean age of the patients was 53.7 ± 12.8 years, and the female/male ratio was 8 (73%)/3 (27%). Of the 11 patients, 9 (82%) had solitary nodules and 2 (18%) had multiple nodules. The mean nodule size was 27 ± 18 (range, 9-70) mm. The mean preoperative TSH level was 1.1 ± 1.0 mIU/L. In terms of the surgical technique, total thyroidectomy and central lymph node dissection were performed in four (36%) patients and total thyroidectomy and lateral lymph node dissection in four (36%) patients. In three (27%) patients, an intraoperative frozen section was performed because the patient did not have a preoperative diagnosis of MTC but had high calcitonin and CEA levels. Total thyroidectomy and central lymph node dissection were performed in these patients as the analysis of the frozen section revealed malignancy (Table 1). The median calcitonin and CEA levels were 898 (range, 10.9-1747) pg/mL and 98.1 (range, 44-196) ng/mL, respectively. At 1 month and 1 year postoperatively, the median calcitonin and CEA levels in the patients were 3.4 (0.7-450) pg/mL and 2.9 (1.9-102) ng/mL and 0.97 (0.4-524) pg/mL and 2.2 (1.1-164) ng/mL, respectively. Although there was a significant difference between preoperative calcitonin levels ($p < 0.001$) and the calcitonin levels at 1 month and 1 year postoperatively ($p = 0.032$), there was no significant difference between the calcitonin levels at 1 month and 1 year postoperatively ($p = 0.602$). Also, there was a significant difference between preoperative CEA levels ($p = 0.002$) and the CEA levels at 1

month and 1 year postoperatively (p = 0.009); however, no significant differences were noted between the CEA levels at 1 month and 1 year postoperatively (p = 1.000; Table 2). The demographic characteristics of the patients are given in Table 1. In preoperative neck ultrasonography), four (36%) patients were classified as TR3 (mildly suspicious), four (36%) as TR4 (moderately suspicious), and three (27%) as TR5 (very suspicious) according to the American Society of Radiology (ACR)-Thyroid Imaging Reporting and Data System scoring system. Based on preoperative fine-needle aspiration biopsy (FNAB) results, two (18%) patients were classified as Bethesda 2 and one (9%) as Bethesda 4 and eight (73%) patients had MTC. When the immunohistochemical findings were examined from the pathology reports of the patients, the amyloid deposits and CEA and calcitonin levels were strongly positive in 10 (91%) patients and weakly positive in 1 (9.1%). All patients were strongly positive for chromogranin but negative for thyroglobulin. According to postoperative pathology reports, seven (64%) patients were in the early stage and four (36%) were in the localized advance stage. Of all patients, 1 (9.1%) had RET-positive hereditary MTC and 10 (91%) had sporadic MTC. During the follow-up, one (9.1%) patient died because of lung metastasis.

Table 1. Patient demographics.

Age (years)	53.7 ± 12.8
Sex	
Female, n (%)	8 (73)
Male, n (%)	3 (27)
Number of nodules	
Solitary, n (%)	9 (82)
Multiple, n (%)	2 (18)
Size (mm)	27 ± 18
TSH (mIU/L)	1.1 ± 1.0
Surgery	
Total thyroidectomy and central LN dissection, n (%)	4 (36.4)
Total thyroidectomy and lateral LN dissection, n (%)	4 (36.4)
Total thyroidectomy and central LN dissection (after frozen), n (%)	3 (27.2)

Data are mean ± standard deviation and median (interquartile range)

LN: Lymph node, TSH: Thyroid stimulating hormone

DISCUSSION

In 1966, Pearse named the neuroendocrine cells in the thyroid that secrete calcitonin as C cells. Of MTCs, 75% that originate from C cells are sporadic and 25% are hereditary. MTC occurs more frequently between the fourth and sixth decades and is more common in women at a female/male ratio of 3/2 [4,5]. Similar to the literature, our study found that the mean age was 53.7 years and that it was more common in women.

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant disease with a frequency of 1/30,000. MEN2 is divided into three types as follows: MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). Although FMTC is a variant of MEN2A, no other diseases are found in MEN2A and they have a more benign course than other hereditary MTCs [4,6]. Approximately 50% of patients with sporadic MTC have somatic RET point mutations [7]. Although most of the patients were sporadic in our series, RET mutation was detected in one (9.1%) patient. MTC associated with MEN syndromes was not observed in our series, and the patient with RET mutation was diagnosed with FMTC.

Although hereditary MTCs are generally bilateral, multicentric, and have multiple nodules, sporadic MTCs are typically unilateral and have single nodules [4]. Similarly, nine (82%) solitary nodules were observed in our series. MTCs behave more aggressively than other thyroid carcinoma types and have higher lymph node metastasis and recurrence rates. Distant metastases such as lung and bone metastases may occur [8,9]. In our series, there were no patients with distant metastases at the time of diagnosis, although seven (64%) patients were in the early stage and four (36%) in the localized advanced stage (Table 3).

The pathological features of MTCs are more difficult to diagnose, manage, and treat than those of other thyroid cancers. Therefore, there is a need for a multidisciplinary team consisting of endocrine surgeons, radiologists, medical

Table 2. Laboratory findings.

Preoperative calcitonin (pg/mL)	Postoperative 1 month calcitonin (pg/mL)	Postoperative 1 year calcitonin (pg/mL)	P	Preoperative CEA (ng/mL)	Postoperative 1 month CEA (ng/mL)	Postoperative 1 year CEA (ng/mL)	P
898 (10.9-1747)	3.4 (0.7-450)	0.97 (0.4-524)	< 0.001	98.1 (44-196)	2.9 (1.9-102)	2.2 (1.1-164)	0.002

Table 3. Medullary thyroid carcinoma and our series.

	Medullary thyroid carcinoma (%)	Our series (%)
Sporadic	75	91
Hereditary	25	9.1
With MEN		
2A	95	-
2B	4-5	-
Without MEN: familial medullary thyroid carcinoma	Rarely	9.1
Stage of medullary thyroid carcinoma		
Early stage	50	64
Advanced stage		
Localized	35	36
Systemic	15	-

MEN: Multiple endocrine neoplasia

oncologists, and pathologists. Despite advanced imaging methods and FNAB, preoperative MTC diagnosis could not be made in three patients in the present study. Intraoperative frozen section was performed in these patients because their preoperative calcitonin and CEA levels were high. Central lymph node dissection was added to total thyroidectomy after the pathologist reported that the analysis of the frozen section revealed malignancy.

Sporadic MTC usually occurs as a solitary thyroid nodule (35-50%) or enlarged lymph nodes. There is limited information in the literature regarding prominent ultrasonography features suggestive of MTC. It is not different from other thyroid carcinomas, except for that round or oval shapes are more common [10]. In our study, four (36%) patients were classified as TR3 (mildly suspicious), four (36%) as TR4 (moderately doubtful), and three (27%) as TR5 (very suspicious) according to the ACR-Thyroid Imaging Reporting and Data System scoring system published by the ACR, which classifies the risk of nodule malignancy in ultrasonography findings [11].

The cytological appearance of MTC varies and may be misdiagnosed because it is similar to follicular neoplasm, sarcoma, or plasmacytoma. The accuracy of FNAB varies in the literature, and diagnostic failure has been reported in 44% of cases [12,13]. Although eight (73%) patients had MTC according to the preoperative FNAB results in our study, two (18%) patients were classified as Bethesda 2 and one (9.1%) as Bethesda 4.

Calcitonin and CEA secretions are directly proportional to the amount of C cells. Although the measurement of calcitonin is controversial in all patients with thyroid nodules, both calcitonin and CEA levels should be measured when the diagnosis of MTC is made by FNAB [14,15]. A calcitonin level of 60-100 pg/mL can be suggestive of MTC. Although the calcitonin levels are normal, an elevated CEA level may indicate MTC. Although CEA is not a specific biomarker for MTC, it is useful in following up the disease [16]. In our study, the mean serum calcitonin and CEA levels were quite high at the time of diagnosis. Except for that in one (9.1%) patient who developed lung metastasis, both markers decreased significantly in all patients at 1 month and 1 year postoperatively.

DNA analysis should be conducted to evaluate RET mutations, and if this mutation is present, pheochromocytoma and hyperparathyroidism should be looked for. The British Thyroid Society recommends investigating pheochromocytoma and hyperparathyroidism in all patients with MTC [17]. In our study, no concomitant endocrine disease was detected in the patient with an RET mutation.

If there is a suspicion of distant metastasis, systemic imaging methods should be used. Recommended imaging studies include ultrasonography, computed tomography, magnetic resonance imaging, and bone scintigraphy. Integrated 18F-fluorodeoxyglucose positron emission tomography is not recommended because of its low sensitivity in detecting metastases [18]. Although distant metastasis was not detected in any of our patients at the time of diagnosis, lung metastasis-related death occurred in one (9.1%) patient during follow-up.

MTC is diagnosed by surgical pathology and produces a distinct accumulation of amyloid (preprocalcitonin), which is very characteristic. They can also occur in different morphologies. Diagnosis must be confirmed by immunohistochemistry positive for chromogranin, calcitonin, and CEA. Although all of these are useful for postoperative surveillance, thyroglobulin has no value in detection [16]. According to the immunohistochemical findings from the pathology reports in our study, the amyloid deposits and CEA and calcitonin levels were strongly positive in 10 (90.9%) patients and weakly positive in 1 (9.1%). In addition, all patients were strongly positive for chromogranin and negative for thyroglobulin.

Standard treatment for MTC is total thyroidectomy and central lymph node dissection. We performed total thyroidectomy and lateral lymph node dissection in four patients and total

thyroidectomy and central lymph node dissection in seven patients. Intraoperative frozen section was performed in three patients because there was no preoperative diagnosis of MTC, but the calcitonin and CEA levels were high. Since the analysis of the frozen section revealed malignancy, central lymph node dissection was added to total thyroidectomy in these patients.

Unlike other thyroid malignancies, MTCs do not respond to radioactive iodine therapy. The surgery type depends on factors such as primary tumor size, lymph node size, and distant metastases. Extended neck surgery is not recommended in the presence of advanced metastatic disease, and palliative interventions to increase the quality of life of patients are preferred [8,19,20].

CONCLUSION

Endocrine surgeons always keep in mind rare thyroid tumors such as MTC. For the preoperative diagnosis of MTC, clinical characteristics, imaging findings, cytology test results, and genetic test results as well as serum calcitonin and CEA levels should be comprehensively evaluated. As a clinical approach, obtaining preoperative calcitonin and CEA measurement for patients with thyroid nodules scheduled for thyroidectomy is advisable. In addition, genetic tests should be performed in all sporadic MTC cases and in the families of germ mutation cases.

Ethics Committee Approval: Approval for the study was obtained from the hospital ethics committee.

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