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Aliyeva N.
National Center of Oncology, Baku, Azerbaijan

Medullary Thyroid Carcinoma: Epidemiology, Diagnosis and Treatment

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Contacts: baku_oncolab@mail.ru

Abstract

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor that represents <5% of all thyroid malignancies and is more aggressive than differentiated thyroid cancer [1]. This review focuses on updates in biochemical testing, early diagnosis, hereditary disease and surgical management. Based on the information obtained we will see importance to diagnose MTC at earlier stages of disease, predict when patients with a hereditary syndrome may develop MTC, perform optimal initial surgery with appropriate lymphadenectomy.
Keywords: medullary thyroid carcinoma, neuroendocrine tumor, parafollicular tests, C-cells, APUD cells, pheochromocytoma, MEN 2 syndrome, calcitonin, procalcitonin, RET mutations, thyroidectomy

Алиева Н.
Национальный онкологический центр, Баку, Азербайджан

Медуллярный рак щитовидной железы: эпидемиология, диагностика и лечение

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Контакты: baku_oncolab@mail.ru

Резюме

Медуллярная карцинома щитовидной железы (МКЩЖ) представляет собой нейроэндокринную опухоль, на долю которой приходится <5% всех злокачественных новообразований щитовидной железы, и она более агрессивна, чем дифференцированный рак щитовидной железы [1]. Данный обзор посвящен обновлениям в биохимическом тестировании, ранней диагностике, наследственным заболеваниям и хирургическому лечению. На основе полученной информации отмечена важность диагностики МКЩЖ на более ранних стадиях заболевания, прогнозирования развития МКЩЖ у пациентов с наследственным синдромом, выполнения оптимальной начальной операции с соответствующей лимфаденэктомией.

Ключевые слова: медуллярная карцинома щитовидной железы, нейроэндокринная опухоль, парафолликулярные тесты, С-клетки, APUD-клетки, феохромоцитома, синдром MEN 2, кальцитонин, прокальцитонин, мутации RET, тиреоидэктомия

■ INTRODUCTION

Medullary carcinoma of the thyroid gland was first described in 1959 (Hazard, Hawk and Crile, 1959) [2]. It arises from the parafollicular cells of the thyroid gland (Williams, 1966) [3]. These cells, now known as C-cells, are derived from the neural crest and secrete the peptide hormone, calcitonin. MTC is essentially a neuroendocrine tumor and is classified as part of apudomas.

APUDomas, currently known as neuroendocrine tumors (NETs), are a group of heterogeneous tumors that arise from the diffuse neuroendocrine system. They occur mainly in the gastrointestinal tract and lungs [4]. To avoid the advancement and progression of such tumors, they should be diagnosed and treated early. APUD tumors arise from APUD cells wich have ability of amine precursors uptake and intracellular decarboxylation, before converting them into active amines, hence the name, amine precursor uptake, and decarboxylation cells. These cells were originally described by Pearse in the 1960s, to arise from the neural crest [5]. The exact cause of NETs remains unknown, many risk factors such as smoking, genetic defects, and immunomodulation have been implicated. Cells in APUD system are adenohypophysis, neurons of hypothalamus, c-cells of thyroid, chief cells of parathyroid, adrenal medullary cells.

MTCs are usually solid well-circumscribed tumors of variable size. Hereditary MTCs are often bilateral and multifocal; these features are less common in sporadic MTC. This is thought to be secondary to the higher incidence of C cell hyperplasia in the hereditary forms [6].

■ EPIDEMIOLOGY

Thyroid cancer is one of the most common malignant endocrine glands worldwide. Papillary and follicular cancers make up 90% of thyroid cancer [7]. Medullary thyroid cancer (MTC) accounting for 3% to 10% of cases [3], and anaplastic thyroid cancer accounting for 1% to 2% of cases. The main reasons for this difference in female than male are polymorphism role in female estrogen receptors. Estrogen also significantly increases the amount of cell proliferation in cancerous thyroid cells compared to the male hormone. The most common age of the thyroid cancer is seen in the fifth and sixth decades of life. While other thyroid cancers primarily affect middle-aged adults, MTC occurs in younger adults (18–25 years of age). However, some patients with MTC can go undiagnosed for decades as the disease progresses slowly with minimal physical symptoms, until the tumor has metastasized or grown large enough to affect the surrounding vasculature. Gender, age, weight, diabetes mellitus, obesity, height, exposure to ionizing radiation, tumour size, lifestyle, genetic and hormonal factors play an important role in thyroid cancer pathogenesis.

Since the 1990s, thyroid cancer incidence has risen in most developed countries, such as the United States, Canada, France and Australia, and has doubled. The reports also

confirmed the incidence of cancer in Asians. It is possible that this increase in the number of thyroid cancer cases is due to the improvement of diagnostic methods or further exposure to unknown risk factors.

The incidence of MTC varies across countries. MTC accounts for 1% to 2% of thyroid cancers in the United States and 1% to 3% in the United Kingdom. In China the proportion of patients diagnosed with PTC (papillary thyroid cancer) had increased from 2004 to 2013, however, the percentage of MTC cases decreased during this same period from 2.03% to 0.42% [8]. As Azerbaijan is an iodine deficit zone, thyroid cancer is common.

■ CLINICAL FEATURES

The occurrence of the tumor may be sporadic or familial, the latter often being associated with pheochromocytoma (Sipple, 1961) it is known as Sipple syndrome [9]. In this familial form, which has an autosomal dominant inheritance (Schimke and Hartmann, 1965), calcitonin concentrations tend to be lower than in sporadic cases, and a small but significant number of patients have basal concentrations that are within the physiological range (Deftos, 1974).

Patients with sporadic MTC may present with palpable thyroid nodules and neck nodes. Larger tumors may result in dyspnea, dysphagia, or hoarseness. Patients with hereditary MTC may have a positive family history or present with clinical features of other components of the MEN 2 syndrome. Pheochromocytomas associated with MEN 2A are more often multicentric (36–58%) and bilateral (40–94%) compared with their sporadic forms [10]. Hyperparathyroidism in MEN 2A is usually asymptomatic [11]. MTC occurs in almost 100% of MEN 2B cases and tends to be more aggressive (increased nodal and distant metastases) compared with MTCs associated with MEN 2A [12]. Rarely, MTC may occur in families without evidence of any other components of MEN 2 syndrome, a condition termed "familial MTC". Activating point mutations in the RET (Rearranged during Transfection) proto-oncogene, located on chromosome 10q11, is responsible for these diseases, whereas somatic RET mutations occur in approximately 60% of patients with sporadic MTC. The RET encodes a receptor tyrosine-kinase, wich is expressed in the cells originating from the neural crest. An additional group of patients with sporadic MTC may have somatic mutations of HRAS, KRAS, or nRAS. RAS mutations have been identified in 10–15% of sporadic MTC cases [13]. Knowledge of the type of RET mutation enables physicians to diagnose, stratify risk, predict prognosis, and choose appropriate management. Patients with RET mutations associated with the highest risk are treated more aggressively than are patients with mutations associated with less-aggressive biology.

■ BIOCHEMICAL DIAGNOSIS

Calcitonin, wich is produced by the parafollicular C cells of the thyroid gland, serves as an excellent biomarker for MTC and is increased in 98–99% of MTC [14]. The serum calcitonin level is not only a sensitive marker for diagnosis but also can predict nodal metastasis and guide treatment. However, elevated CT may be induced by several conditions such as small cell lung, breast and pancreatic cancers, neuroendocrine tumors, renal failure, sepsis, smoke or alcohol consumption, proton-pump inhibitor therapy. Moreover, non-medullary thyroid diseases, such as follicular cancers, goiter and autoimmune thyroid diseases could be associated with mild-moderate CT increase.

Measuring calcitonin (CT) levels enabling its diagnosis in earlier stages and improving the prognosis. CT is a 32-amino-acid hormone biosynthesized from the polypeptide precursor procalcitonin (PCT), a 116-amino-acid prohormone.

Procalcitonin (PCT) is a CT precursor found at low serum concentrations in healthy individuals, which increases in systemic inflammation, infection and sepsis [15]. More recently, PCT has been preliminarily shown to be an accurate additional marker to CT in MTC diagnosis and follow-up, with the advantagesof better in vitro stability and consistency of analytical methods [16, 17]. It has an excellent stability, with a half-life of about 20–24 hours irrespective of its concentration, and no need to be kept on ice after collection. Additionally, no or only marginal increase of serum PCT was observed after PG infusion in patients with non-medullary diseases but increased basal serum CT. Currently, no prospective data on the addition of PCT measurement in patients with thyroid nodules and increased CT are available.

Serum carcinoembryonic antigen (CEA) is another useful biomarker for MTC, especially in patients with poorly differentiated metastatic MTC who may not have elevated serum calcitonin levels. In hereditary MTC associated with MEN 2 syndromes, evaluation of urine metanephrines or vanillylmandelic acid and serum calcium and parathyroid hormone is useful for diagnosing pheochromocytoma and hyperparathyroidism.

RET mutation is present in all of the cells (a germline mutation) and these mutations cause the development of MTC. Whether MTC is sporadic or familial can be determined by a blood test for the RET protooncogene [18]. Anyone diagnosed with MTC should have this test run to determine whether the MTC is familial (meaning other family members may also have MTC that has not yet been diagnosed) or sporadic.

■ SURGERY TREATMENT

The main treatment tactic for patients diagnosed with medullary cancer is surgical method. Because in all patients with hereditary form and in 30% of patients with sporadic form, the disease is multifocal at the time of initial examination [19]. Before surgery, the mobility of the vocal cords and the proximity of neurovascular structures to the gland should be assessed. ATA guidelines recommend central lymph node dissection in patients undergoing total thyroidectomy. This is due to the high incidence of lymph node metastases, the occasional failure to detect metastases during imaging, and the negative effects of reoperation on the course of the disease.

■ PROGNOSIS

Several factors portend an adverse outcome in patients with MTC. Poor prognosis is associated with older age, advanced disease at the time of diagnosis of a large primary tumor, lymph node metastases, markedly elevated serum levels of CTN and CEA preoperatively, extrathyroidal invasion of the trachea or soft tissues, and distant metastases. If calcitonin levels return to normal after surgery, the survival rate is predicted to be 97.7% [20].

Patients with MEN 2B and patients with MEN 2A who have RET mutations in codon 634 have a poorer prognosis than those with RET mutations in other codons. Also, in patients with sporadic MTC, the presence of a RET M918T mutation, compared with other codon mutations, is associated with a more aggressive tumor and a poor prognosis [9].

Patients apparently cured by thyroidectomy are followed at 6-month intervals with measurement of serum levels of CTN and CEA. The doubling times of serum CTN are especially useful in predicting the course of the disease [21]. CTN doubling times of less than 6 months (com-pared with those greater than 24 months) are associated with a very poor prognosis [22].

■ MATERIALS AND METHODS

We evaluated the results of the calcitonin test analyzed in the laboratory of our center (National Center of Oncology) during 2018–2023. Over a 5-year period, 1373 test results were reviewed, and 278 pathological results were detected. 100 of the pathological results were in men and 178 in women. Very high results (above 1000 pg/ml) were observed in 118 cases.

The analyzes were performed on the Roche Cobas e601 fully automatic device using the ECLIA (electrochemiluminescence immunoassay) method. All samples were centrifuged at 4000 rpm, 15 °C, for 10 minutes, and serum was obtained. Normal values were <9.82 pg/ml for women and <14.3 pg/ml for men. The USG, FNAB, histological and immunohistochemical results of the patients' were also reviewed.

■ RESULTS

We selected 66 patients and grouped their medical history, preoperative and postoperative calcitonin results, metastases and recurrences, and other diseases. Patients over 30-40 years of age predominated in terms of age. Percentages by age are given in table number 1.

The presence of lymph node metastases, distant metastases and recurrences in patients was studied. Lymph node metastases were found in 35 (53.03%) patients, and

Table 1
Incidence of patients depending on age

Age	0–17	18–30	30–40	40–50	50–60	Above 60
Number of patients	1	10	13	15	15	12
%	1,51	15,15	19,70	22,73	22,73	18,18

Table 2
Incidence of metastases and recurrences

Organs	Num.of patients	%
Lymph	35	53,03
Lymph and lungs	4	6,06
Lymph and adrenal glands	3	4,55
Lymph and mediastinum	4	6,06
Lymph and liver	2	3,03
Lymph and bones	2	3,03
Bones	2	3,03
Mediastinum and liver	1	1,52
Ovarian and liver	1	1,52
Recurrences	20	30,3

Table 3
Incidence based on calcitonin test

Calcitonin result	Up to 2000 pg/ml		Above 2000 pg/ml	
Number of patients	43	76,79%	13	23,21%

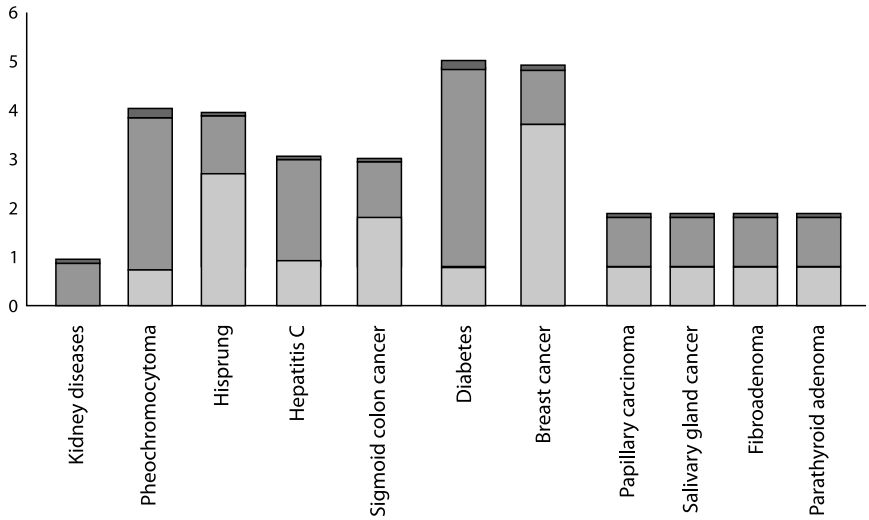
lymph node and distant organ metastases were found in 15 (22.73%) patients. Distant organs that metastasize were lungs, adrenal glands, septum, liver and bones. Recurrence was found in 20 (30.3%) of the patients included in the study. Table 2 shows the regional and distant metastases and recurrences.

According to the calcitonin test, patients were divided into 2 groups with results up to 2000 pg/ml and above 2000 pg/ml. 43 (76.79%) patients with results up to 2000 pg/ml and 13 (23.21%) patients with results above 2000 pg/ml were noted. The results are shown in Table 3.

In patients diagnosed with medullary thyroid cancer were detected other oncological, endocrinological, infectious, etc. diseases. These diseases are listed in the diagram below.

RET/PTC1 and RET/PTC3 were analyzed in 16 patients, and the results were positive in 6 patients. Two of the patients are brothers, the other two are sister and brother. Among the patients whose RET analysis was not checked, we have patients were mother and son diagnosed with medullary cancer. Among RET-positive patients, those who underwent surgery in the early stages had better quality of life and disease progression. We keep these patients and their close relatives under dynamic control.

We have observed rare results in patients operated on in the Head and Neck Tumor department of our center. We called them "miracles". One patient had a preoperative calcitonin result of 1492 pg/ml. After the operation performed by Professor A. Aliyev, the patient's calcitonin result was 3.77 pg/ml.



Associated diseases rate

Nəticə №	: 1608250	Kart №	: Y230013610
Adı Soyadı	:	İstək vaxtı	: 20.07.2023 09:35:40
Doğum Tar.cinsiyyəti	: 4.06.1985 -Qadın	Barkod çap vaxtı	: 20.07.2023 09:43:46
Sənəd №	: L0090177 - AA1990880	Küm. qəbul vaxtı	: 20.07.2023 10:07:09
Göndərən Həkim	:	Həkimi	: Əziz Əliyev CƏMİL
Şöbə Adı	: NÜVƏ TƏBABƏTİ VƏ RADİONUKLİD TERAPİYA		

İmmunokimyəvi analizlər — İşlənmə Vaxtı: 20.07.2023 11:43 Təsdiq vaxtı: 20.07.2023 11:43

Analiz Adı	Nəticə	Ölçü Vahidi	Norma	Əvvəlki nəticələri
CEA - Onkomarker	4.95	ng/ml	H(0 - 4.5)	-
TSH	2.64	mU/l	N(0.4 - 4.2)	1.98 - 13/06/2023
Kalsitonin	0.659	pg/mL	N(<9.82)	1800 - 13/06/2023

Nəticə №	: 1688792	Kart №	: Y240002095
Adı Soyadı	:	İstək vaxtı	: 12.02.2024 09:37:08
Doğum Tar.cinsiyyəti	: 27.07.1987 -Kişi	Barkod çap vaxtı	: 12.02.2024 10:52:30
Sənəd №	: L0213312 - MYİ 0642195	Küm. qəbul vaxtı	: 12.02.2024 11:01:19
Göndərən Həkim	:	Həkimi	: Əziz Əliyev CƏMİL
Şöbə Adı	: BAŞ-BOYUN ŞİŞLƏRİ ŞÖBƏSİ		

İmmunokimyəvi analizlər — İşlənmə Vaxtı: 12.02.2024 14:55 Təsdiq vaxtı: 12.02.2024 14:57

Analiz Adı	Nəticə	Ölçü Vahidi	Norma	Əvvəlki nəticələri
Kalsitonin	3.77	pg/mL	N(<14.3)	1492 - 25/01/2024

The other patient's preoperative blood calcitonin value was 1800 pg/ml. So after the operation this value decreased to 0.659 pg/ml.

The above cases demonstrate the importance of proper surgical treatment for medullary cancer.

■ CONCLUSION

The prognosis of medullary thyroid cancer is better if it is detected in the early stages. In order to detect the disease at an early stage, laboratory tests should be analyzed in addition to instrumental examination methods. Calcitonin analysis is informative not only for early detection, but also for monitoring the disease and for postoperative follow-up. Patients diagnosed with MTC should be screened for RET analysis to rule out hereditary forms. Relatives of patients with RET positive status should undergo follow-up examinations. Surgery performed at an early stage has a positive effect on the patient's survival time.

Considering all the above, it is important to educate people, especially patients diagnosed with MTC. This is precisely the purpose of the research we conduct, the analyses we do, and the articles we write.

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