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Case Report

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Serum Calcitonin Levels may be Used in the Differential Diagnosis of Vagal Glomus

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ABSTRACT

Medullary thyroid carcinoma (MTC) is a neuroendocrine (NE) tumor and is very rarely observed. MTC originates from the parafolliculer C cell and can show various histopathological patterns. Head and neck paragangliomas are seen rarely. Paragangliomas in the head and neck region are usually non-functional. MTC should be considered in the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical investigation is needed to determine the rare potential etiology underlying this condition. Because patients with MTC can present different clinical manifestations, otolaryngologist must be aware of MTC and its rare medical presentations. This case presented here highlights the importance of serum calcitonin levels in the differential diagnosis of paragangliomas in the head and neck region.

KEY WORDS: Calcitonin; Medullary thyroid cancer; Glomus vagale.

ABBREVIATIONS: MTC: Medullary Thyroid Carcinoma; NE: Neuroendocrine; US: Ultrasonography; CEA: Carcinoembryonic antigen; SEER: Surveillance, Epidemiology, and End Results.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a neuroendocrine (NE) tumor and comprises lesser than 10% of all thyroid malign tumors. So it is a very rarely occuring tumor in all malignancies.[1-3] Due to recent Surveillance, Epidemiology, and End Results (SEER) data in the United States, MTC accounts for 1% to 2% of all thyroid cancers.[4,5] A large part of the medullary carcinomas are sporadic, and familial form constitutes nearly 25%.[4-6] The 10-year survival rate of MTC is approximately about 75% with respect to current literature. The study of Jung et al[7] reported that the 5- and 10-year survival rates for MTC were 92% and 87%, respectively. The MTC spreads early to both paratracheal and lateral cervical lymph nodes, and distant spreading occurs in the liver, lungs, bones, and less frequently in brain and skin. All the patients undergoing a pre-operative diagnosis of MTC should be evaluated with a detailed neck ultrasonography (US) and measurement of serum calcitonin and carcinoembryonic antigen (CEA). Basal serum calcitonin concentrations usually can be linked to tumor burden but also indicates tumor differentiation in MTC.[8-10]

MTC is a neuroendocrine cancer that originates from the parafollicular C cells and can indicate various histopathological patterns. One of these is a paraganglioma-like pattern.[9,11] Another type of NE cancer is an extra-adrenal parasympathetic paraganglioma that is usually found in the head and neck region. These type of paragangliomas are usually non-functional tumors (95%).[8] Paragangliomas constitute nearly 0.6% of all head and neck tumors and they orig-

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inate from the vagus nerve ganglion, carotid body, jugular bulb and tympanic plexus.[12] The differential diagnosis of neuroendocrine tumors appear to be quite difficult in certain unusual clinical presentations. Preoperative fine needle aspiration biopsies provide the results for the early diagnosis of MTC. Biochemical and genetic screening would also help determine patients with early stage sporadic MTC. However, FNAB is never excluded from a malignancy and sometimes proves to be inadequate in the differential diagnosis of MTC. The reported case illustrates a valuable example of what needs to be done in a similar situation. MTC should be considered in the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical investigation is needed to determine the rare potential etiology underlying this condition. To the best of our knowledge, this is the first case reported in the literature to focus on the differential diagnosis of MTC with serum calcitonin levels.

CASE PRESENTATION

A 25 year old female patient reported to our clinic with a 3 cm mass in level 4 of the left side of her neck. She noticed 3 months ago that the mass showed a tendency to grow. On performing clinical investigation, there was no medical evidence other than a mass in the neck. No pathological findings were observed following the pan endoscopic examination. A mass of About 3 cm size in the left side of the neck was revealed in the ultrasonography (USG) reports. A diffuse echo reduction and, pseudonodular image in the thyroid gland was observed in the USG report. On performing the MRI of the neck, a 40×23 mm sized, well-circumscribed mass was seen that displaced the left common carotid artery and jugular vein to the anterior and the right. This mass showed intense contrast enhancement and vascular structures were observed in the mass. This view was consistent with the observation of the glomus vagale radiologically. No pathological finding was observed in the thyroid gland and other neck structures (Figure 1). Because glomus tumors are generally seen at level 2-3, radiological diagnosis of glomus tumor was viewed with medical suspicion. For this reason, a fine needle aspiration biopsy (FNAB) was performed. FNAB was also found to be compatible with the vagal glomus and the patient was referred to the endocrinology clinic. The 24-hour analysis of adrenaline, noradrenaline, vanilmandelic acid, metanephrine, normetanephrine, dopamine and, 5-hydroxyindolacetic acid levels in the urine were observed to be in the normal range, where upon the patient was operated with the diagnosis of the non-functioning of the glomus vagale tumor to the left. While performing the surgery, the mass in close relation with the vagina carotica was extended into the carotid sheath posterolaterally. When the mass was dissected, it was observed that there was no direct relation with any structure in the carotid sheath and, the mass could be easily stripped from the vagus. Thereupon, the mass was subjected to frozen examination with the consultation of the pathologist. In the opinion of the pathologist, the mass was a neuroendocrine tumor and a glomus tumor and thyroid medullary cancer was observed following differential diagnosis. Palpation of the thyroid gland, and assessment of level 6 and level 4 was performed intraoperatively. Because of the lack of any pathological symptom during the intraoperative assessment, it was decided that before undertaking any further action, a definitive pathological report had to be obtained. In the definitive pathological examination, with chromogranin, synaptophysin and calcitonin by immunohistochemical staining, the reports following diagnosis were indicative of medullary thyroid cancer metastases (Figure 2). After pathological examination, we assessed the level of serum calcitonin and this was recorded as 809 pg/ml (n:0-5). Total thyroidectomy, bilateral functional neck dissection and level six neck dissection were decided to be performed by the endocrine surgery council. The operation was completed without any complications. Once, three of the four parathyroid glands were observed and confirmed by frozen examination, which were replanted to the left sternocleidomastoid muscle 1/3 middle segment. Postoperatively, bilateral vocal cord movements were normal, but to address the cause of hypocalcemia, calcium 2×1500 mg and 1×0.25 mcg calcitriol® had to be administered. In the post-operative pathological report; four focus micromedullary thyroid cancer, four metastasis in the

Figure 1: Neck Contrast Enhanced Magnetic Resonance Imaging.

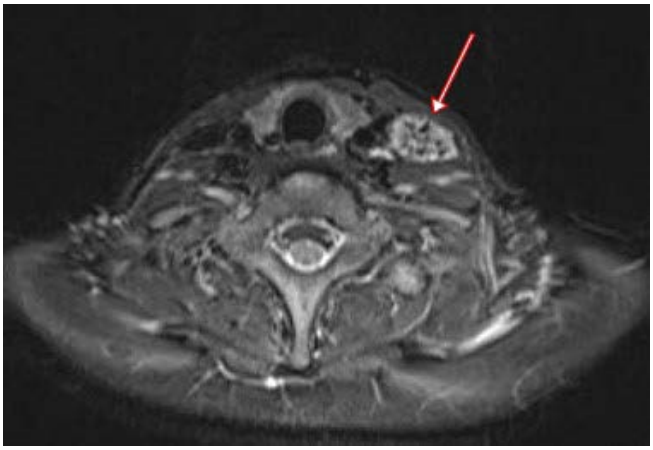

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Figure 2: Medullary Thyroid Carcinoma Metastasis, Including Amyloid Deposits that Infiltrate the Lymph Node in the Environment with Follicular Hyperplasia (4x).

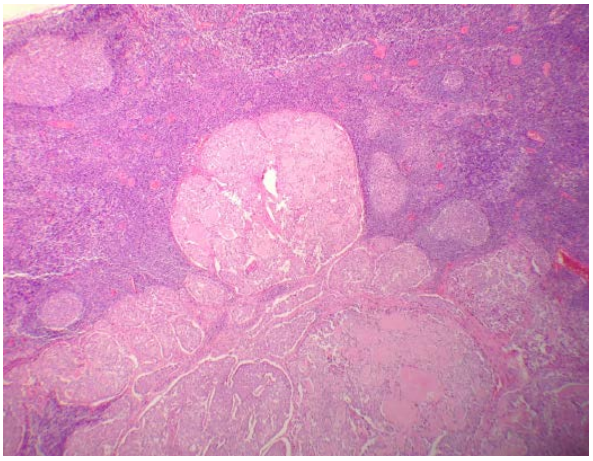
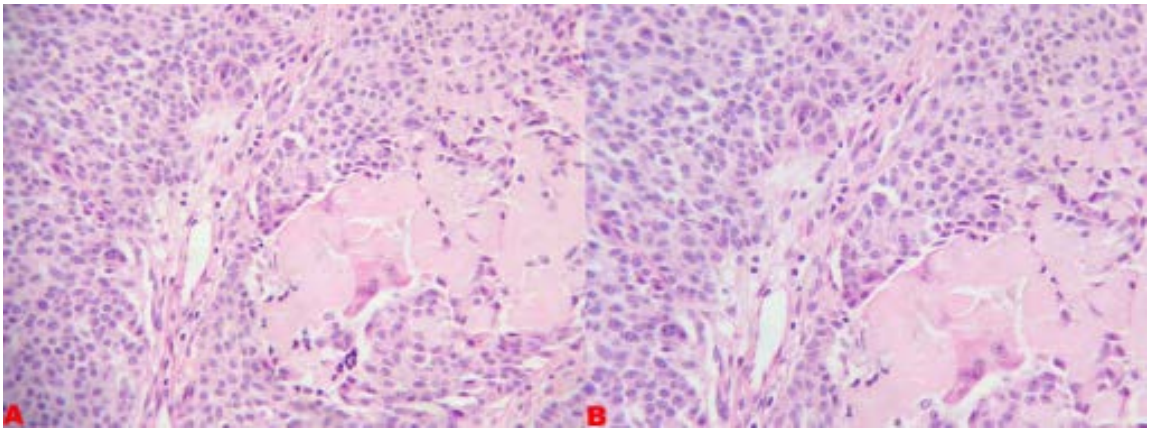


Figure 3: A) The Tumor, Composed of Cells with Uniform Mononucleolide with Salt Pepper Chromate and Amyloid Accumulation is Observed in the Lower Right Corner (40x). B) Tumor Tissue, Composed of Cells with Large Single Nucleolus and, Salt Pepper Chromatin Structure and, Large Eosinophilic Material Accumulation (40x).



central neck dissection specimen and, pericapsular invasion in one of these four metastasis and, one metastasis with pericapsular invasion in the right neck dissection specimen was revealed (Figure 3A-3B). When the calcium and rocaltrol® treatment was terminated in the first month following the surgery, the serum calcium level remained stable at 8.25 mg/dL. In the early follow-up period, pregnancy occurred. Thus, adjuvant therapy was not administered. The patient is still followed up regularly without any sign of distant metastasis and local recurrence as has been observed in the imaging findings but the serum calcitonin level has been recorded at 66.20 pg/mL (n:0-5)

DISCUSSION

An elevated serum calcitonin level is a highly sensitive and specific tumor marker for postsurgical follow-up of patients with MTC following total thyroidectomy. However, relative to more advanced tumors, which may be dedifferentiated by decreased calcitonin production, CEA may be a more worthy tumor marker.[13] Other important prognostic factors for adverse outcome include advanced age at diagnosis, extent of primary tumor, and nodal metastasis and distant metastases.[14] Standard treatment for patients with MTC is total thyroidectomy and dissection of cervical lymph node (LN) compartments, depending on serum calcitonin levels and neck US findings. Usually in sporadic MTC, the tumor is unifocal and defined in the fifth or sixth decade of life. In the hereditary MTC, a vast majority of patients are asymptomatic initially and diagnosed by genetic or biochemical screening tests during the early stages of the disease. The clinical symptoms of sporadic MTC contain a thyroid nodule or mass, cervical lymphadenopathy or other cervical symptoms, metastatic disease, and seldom diarrhea, flushing, or Cushing's syndrome due to chronic ectopic adrenocorticotropic hormone production.[15-18]

Histopathological differential diagnosis of MTC in-

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cludes paraganglioma and other NE tumors.[10] To distinguish NE tumors on the basis of cytomorphology is difficult. Owing to this reason, clinicians must keep the pathologist informed and immunohistochemistry must be performed.[11] In the diagnosis of MTC, calcitonin, chromogranin A, or CEA immunostaining can be used.[8] Calcitonin is an important molecule because it has a very significant role in the diagnosis and clinical follow-up of patients with MTC.[6] If immunohistochemistry cannot be performed and there is a confusion regarding the diagnosis, the serum calcitonin level can help clarify the diagnostic reports.[7] In particular, the glomus vagale has an origin in the neuroendocrine tumor and can be located anywhere in the vagus ganglia. Other neuroendocrine tumors and metastases of these tumors are observed by differential diagnosis. Especially in the evaluation of the head and neck region glomus tumors, medullary thyroid cancer metastasis is clinical relevant. As has been indicated in this case, such that FNAB and imaging cannot provide relevant information based on the differential diagnosis. Therefore, monitoring the role of calcitonin in preoperative evaluation will be very helpful in the planning of operations, thus preventing from possible secondary operations and eliminating additional risks of morbidity and mortality.

The main causes of death of patients with MTC are distant metastases. Survival after the discovery of distant metastases is 51% in 1 year, 26% in 5 years, and 10% in 10 years according to the existing research literature.[19-21] Long-term survival of the two types of MTC patients was not significantly different. Various factors have been proposed as prognostic factors for the outcome for patients with MTC. Age at diagnosis, TNM stage and completeness of initial surgery are significant factors affecting the outcome.[22,23] Therefore, patients with MTC should be closely followed-up and recommended about related endocrine pathologies and the risk of the disease for other family members.

CONCLUSION

MTC should be considered for the differential diagnosis of paragangliomas in the head and neck region. A high degree of clinical suspicion needs to be observed to determine this rare potential etiology. Because patients with MTC can present with different clinical manifestations, the otolaryngologist must be aware of MTC and its rare presentations.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

INFORMED CONSENT

Written informed consent was obtained from the patient who participated in this case.

REFERENCES

1. Albores-Saavedra J, LiVolsi VA, Williams ED. Medullary carcinoma. *Semin Diagn Pathol*. 1985; 2: 137-146.

2. Wells SA Jr., Franz C. Medullary carcinoma of the thyroid gland. *World J Surg*. 2000; 24: 952-956. doi: 10.1007/s002680010166

3. Matias-Guiu X, De Lellis R. Medullary thyroid carcinoma: A 25-year perspective. *Endocr Pathol*. 2014; 25: 21-29. doi: 10.1007/s12022-013-9287-2

4. Wells SA Jr., Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: An update. *J Clin Endocrinol Metab*. 2013; 98: 3149-3164. doi: 10.1210/jc.2013-1204

5. Wells SA Jr., Asa SL, Dralle H, et al. Revised american thyroid association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015; 25: 567-610. doi: 10.1089/thy.2014.0335

6. Baloch ZW, LiVolsi VA. C-cells and their associated lesions and conditions: A pathologists perspective. *Turk Patoloji Derg*. 2015; 31: 60-79. doi: 10.5146/tjpath.2015.01315

7. Jung KY, Kim SM, Yoo WS, et al. Postoperative biochemical remission of serum calcitonin is the best predictive factor for recurrence-free survival of medullary thyroid cancer: A large-scale retrospective analysis over 30 years. *Clin Endocrinol (Oxf)*. 2016; 84: 587-597. doi: 10.1111/cen.12852

8. Chernock RD, Hagemann IS. Molecular pathology of hereditary and sporadic medullary thyroid carcinomas. *Am J Clin Pathol*. 2015; 143: 768-777. doi: 10.1309/AJCPHWACTTUYJ7DD

9. Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: Pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010; 39: 775-783. doi: 10.1097/MPA.0b013e3181ebb4f0

10. Destito D, Bucolo S, Florio A, Quattrocchi C. Management of head and neck paragangliomas: A series of 9 cases and review of the literature. *Ear Nose Throat J*. 2012; 91(8): 366-375. Web site. http://search.proquest.com/openview/3e1d238ac459837089a213989944ecd6/1?pq-origsite=gscholar&cbl=47886. Accessed January 7, 2017.

11. Canberk Ş, Fırat P, SchmItt F. Pitfalls in the cytological assessment of thyroid nodules. *Turk Patoloji Derg*. 2015; 31: 18-33. doi: 10.5146/tjpath.2015.01312

12. Sivrikoz E, Ozbey NC, Kaya B, et al. Neuroendocrine tumors presenting with thyroid gland metastasis: A case series. *J Med Case Rep*. 2012; 6: 73. doi: 10.1186/1752-1947-6-73

13. Busnardo B, Girelli ME, Simioni N, Nacamulli D, Buset-

ISSN 2470-4059 http://dx.doi.org/10.17140/OTLOJ-3-136

to E. Nonparallel patterns of calcitonin and carcinoembryonic antigen levels in the follow-up of medullary thyroid carcinoma. *Cancer*. 1984; 53: 278-285. doi: 10.1002/1097-0142(19840115)53:2<278::AID-CNCR2820530216>3.0.CO;2-Z

14. Kloos RT, Eng C, Evans DB, et al. American thyroid association guidelines task force. Medullary thyroid cancer: Management guidelines of the American Thyroid Association. *Thyroid*. 2009; 19: 565-612. doi: 10.1089/thy.2008.0403

15. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. *Cancer Epidemiol Biomarkers Prev*. 2013; 22: 1252-1259. doi: 10.1158/1055-9965.EPI-13-0242

16. Oh CM, Jung KW, Won YJ, Shin A, Kong HJ, Lee JS. Age-period-cohort analysis of thyroid cancer incidence in Korea. *Cancer Res Treat*. 2015; 47: 362-369. doi: 10.4143/crt.2014.110

17. Lindsey SC, Ganly I, Palmer F, Tuttle RM. Response to initial therapy predicts clinical outcomes in medullary thyroid cancer. *Thyroid*. 2015; 25: 242-249. doi: 10.1089/thy.2014.0277

18. Schlumberger M, Elisei R, Muller S, et al. Final overall survival analysis of EXAM, an international, double-blind, randomized, placebo-controlled phase III trial of cabozantinib (Cabo) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline. *J Clin Oncol*. 2015; 33(15 Suppl): S6012. Web site. http://meetinglibrary.asco.org/content/147994-156. Accessed January 7, 2017.

19. Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH. Medullary thyroid carcinoma: Clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer*. 2000; 88: 1139-1148.

20. Dottorini ME, Assi A, Sironi M, Sangalli G, Spreafico G, Colombo L. Multivariate analysis of patients with medullary thyroid carcinoma. Prognostic significance and impact on treatment of clinical and pathologic variables. *Cancer*. 1996; 77: 1556-1565. doi: 10.1002/(SICI)1097-0142(19960415)77:8<1556::AID-CNCR20>3.0.CO;2-Y

21. Modigliani E, Cohen R, Campos JM, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: Results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. *Clin Endocrinol (Oxf)*. 1998; 48: 265-273. doi: 10.1046/j.1365-2265.1998.00392.x

22. Figlioli G, Landi S, Romei C, Elisei R, Gemignani F. Medullary thyroid carcinoma (MTC) and RET proto-oncogene: Mutation spectrum in the familial cases and a meta-analysis of studies on the sporadic form. *Mutat Res*. 2013; 752: 36-44. doi: 10.1016/j.mrrev.2012.09.002

23. Raue F, Kotzerke J, Reinwein D, et al. Prognostic factors in medullary thyroid carcinoma: Eevaluation of 741 patients from the German Medullary Thyroid Carcinoma Register. *Clin Investig*. 1993; 71: 7-12. doi: 10.1007/BF00210956