

Case Report**Metastatic medullary thyroid carcinoma: A case report***Mitra Niafar^{*a}, Shahram Dabiri^b, Farshid Bozorgi^c, Farid Niafar^d, Nasrin Gholami^e***Abstract**

Medullary thyroid carcinoma accounts for 4% of thyroid carcinoma and originates from parafollicular cells, secreting calcitonin and carcinoembryonic antigen (CEA). Conventional radiographic modalities such as Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), and Ultrasonography (U/S), are used for detecting recurrences following total thyroidectomy. However, metastatic disease frequently escapes detection by the above modalities, even when its presence is suggested by persistently elevated serum calcitonin levels. In this paper, we report a case of medullary thyroid carcinoma in a 40 year-old woman who had whole body octreotide scintigraphy to evaluate and detect the origin of calcitonin and CEA secretion.

KEYWORDS: Thyroid cancer, Medullary, Calcitonin, Neoplasm metastasis.

JRMS 2011; 16(4): 568–573

Carcinoma of the thyroid is usually of follicular cell origin, but medullary carcinoma arises from the parafollicular or C cells. Four distinct histologic types of follicular cell-derived cancers are recognized.¹ The majority of cases are papillary, with its major subtype follicular variant, and other histologic types are follicular, oxyphilic or Hurthle cell, and anaplastic.

Most of medullary neoplasms are sporadic (80%), although minority of them may occur in hereditary form (Multiple Endocrine Neoplasia type 2 (MEN2)).² Calcitonin is the most sensitive and specific tumor marker at the preoperative diagnosis³ and the post surgery follow up.⁴ Calcitonin values decrease into the normal range after resection of the tumor and regional involvement are regarded as complete tumor regression biochemically.⁵ Total thyroidectomy

is the only successful option for treatment because up to 30% of sporadic MTC and all of the inherited ones are multifocal and bilateral.⁶ Patients should be followed up for residual and recurrent tumor. Elevation of calcitonin at 6 months post-operation is indicative of metastatic or residual disease.⁷ The time of calcitonin assay after operation is important because regression of this substance is slow and it may take several months to reach to the nadir level.⁸ Those with near normal level of calcitonin can be followed, but those with calcitonin level above 100 ng/ml after six months should be evaluated for residual tumor or metastases.⁹ Adequate surgical eradication is the only curative form of therapy for MTC at present. Unlike differentiated thyroid cancers, MTC cells do not uptake iodine, and iodine-131 treatment is ineffective.¹⁰ Patients with progressive or

^a Assistant Professor, Endocrinology and Metabolism Section, Department of Medicine, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

^b Professor, Department of Nuclear Medicine, Imam Khomeini Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

^c Anatomical and Clinical Pathologist, Department of Pathology, Imam Khomeini Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

^d Assistant Professor, Department of Diagnostic Imaging, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran.

^e Resident, Department of Internal Medicine, Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

* Corresponding Author

E-mail: dr_niafar@yahoo.com

symptomatic metastatic disease who cannot be treated by surgery or radiotherapy should be considered candidates for systemic therapy. Current and experimental chemotherapies for advanced medullary thyroid carcinomas include tyrosine kinase (TK) inhibitors such as sorafenib, sunitinib, and pazopanib.¹¹

During past several years, numerous other kinase inhibitors such as vandetanib, XL184, and motesanib have been studied in clinical trials. These drugs remain investigational at this time and are not available for routine clinical use.¹²

Cytotoxic chemotherapy, of which dacarbazine-based regimens such as cyclophosphamide-vincristine dacarbazine are preferable, is an alternative option for patients who cannot tolerate or who fail TK inhibitors.¹³

Immunotherapy of MTC holds some promise, but as yet has had little clinical application. One approach is use of tumor vaccines and another is to administer monoclonal antibodies coupled to radioisotopes to deliver radiotherapy. These therapies have been tried but they remain investigational.¹⁴ Numerous radiopharmaceuticals are currently used for detecting local and distant metastases of MTC such as ¹³¹I or ¹²³I- Meta-iodo-benzyl-guanidine (MIBG), alkaline ^{99m}Tc-Dimercaptosuccinyl acid [DMSA (V)], and ^{99m}Tc-Methoxyisobutylisonitril (MIBI). ^{99m}Tc-DMSA (V) is selectively taken up into sites of primary and metastatic and recurrent sites of medullary thyroid cancer.¹⁵

The presence of high-affinity somatostatin receptors have been demonstrated in most metastatic endocrine tumors. C cells originate from neural crest in embryonic phase and similar to other neuroendocrine tumors contain somatostatin receptors.^{6,16} American Thyroid Association does not recommend somatostatin receptor imaging for the initial evaluation of metastases.¹⁷ Here we report a case of medullary thyroid cancer with mediastinal metastasis that octreotide scintigraphy could help us in localizing the site of calcitonin secretion, whereas other imaging modalities could not localize the metastatic lesion.

Case Report

We report a 40-year-old woman presenting with a single thyroid nodule. She referred to endocrinologist after noticing a swelling on the right side of her neck which had gradually enlarged. There was no relevant family history. During her initial visit to our institution, the patient was in good condition, her blood pressure was 120/80 mm Hg, and her pulse was 80/min and regular. The patient was clinically euthyroid, and the rest of the examination was unremarkable, with the exception of 2 cm firm smooth mass on the right side of the thyroid that moved with swallowing. Thyroid function tests gave normal results. Fine-needle aspiration biopsy (FNA) of the nodule was consistent with a diagnosis of medullary thyroid carcinoma.

There was no family history of MEN2 in our patient and her serum calcium was 9.4 mg/dl.

The patient was referred to a thyroid surgeon and total thyroidectomy with limited cervical dissection was carried out. According to pathology lab report, the tumor was in dimension of 2 cm with focal capsular invasion without any lymph node involvement. Pathologic findings in thyroid gland are showed in the figures 1 and 2, which reveal neoplastic proliferation of parafollicular cells in nesting pattern with amorphous eosinophilic material depositions in stroma that was positive for amyloid staining.

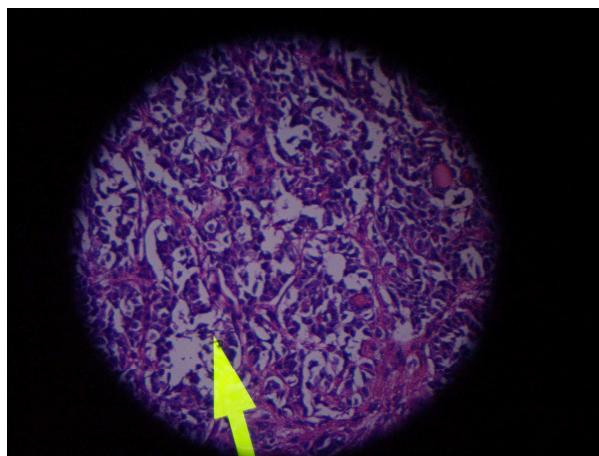


Figure 1. Hematoxylin and eosin (H & E) staining of thyroid tissue with nesting proliferation of neoplastic parafollicular cells with stromal amorphous material deposition

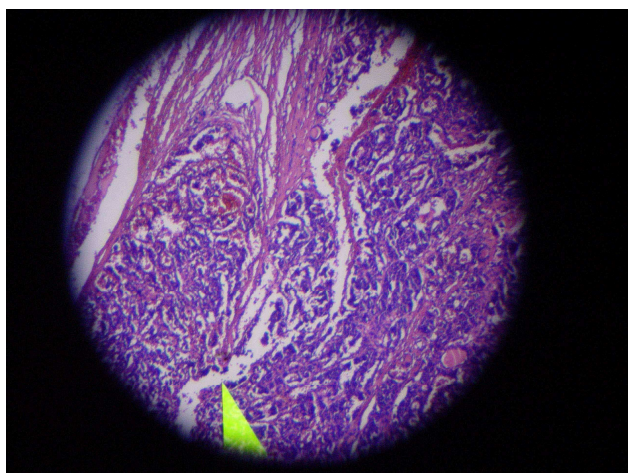


Figure 2. Congo Red staining of thyroid medullary carcinoma show stromal amyloid deposition

She was discharged after the prescription of 100 microgram levothyroxine. Four months later, calcitonin was higher than 2000 pg/ml, CEA = 98 ng/ml (Normal range in non-smoker is less than 3 ng/ml) and TSH was in normal range. In physical examination, 2 cm × 2 cm lymph node was found in the right lateral side of cervical region. With the high suspicion for the metastatic involvement, she underwent cervical lymph node dissection. The pathology confirmed involvement of the lymph nodes with MTC, but 4 months later calcitonin and CEA levels did not decrease (CEA = 44 ng/ml, calcitonin > 2000 pg/ml, TSH = 1.4 mIU/L); however, physical examination was normal. For further evaluation, cervical and chest computed tomography with abdominal and pelvic sonography were done. All the tests were normal except for fatty liver manifestations and one hypoechoic region measuring 29 mm in the left lobe of liver with geographical border. Correlation with CT and normal liver function showed that this area was fat sparing region.

Eight months after the second surgery, serum calcitonin, and CEA levels were elevated and unchanged. Repeat neck, chest, pelvic and abdominal computed tomography were normal. We did ^{99m}Tc-DMSA(V) whole body scan but again no positive finding was

observed. Finally, after consultation with the specialist in nuclear medicine, somatostatin receptor whole body scan (with ^{99m}Tc-HYNIC TOC) was performed through which the origin of calcitonin and CEA secretion was found in the right side of anterior superior mediastinum (Figure 3). She underwent mediastinal lymph node dissection and the same pathologic features also were seen in assessment of mediastinal lymph node which showed in the figures 4 and 5. Four months after the removal of the lymph node in superior anterior mediastinum, the level of the calcitonin and CEA decreased to 69 pg/ml and 12 ng/ml, respectively.



Figure 3. Hematoxylin and eosin (H & E)staining of lymph node infiltrated by neoplastic cells and stromal eosinophilic amorphous depositions

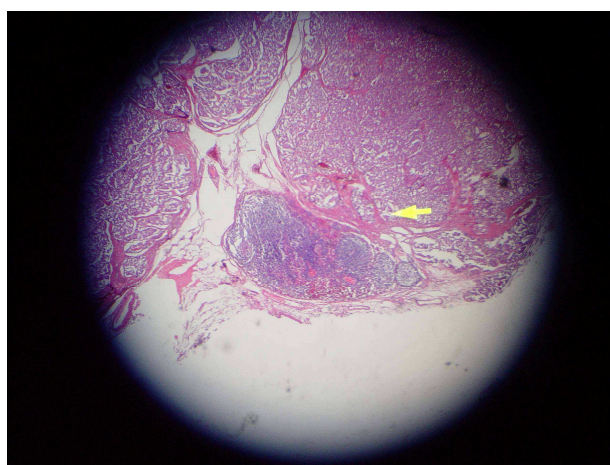


Figure 4. Congo Red staining of lymph node show stromal amyloid deposition

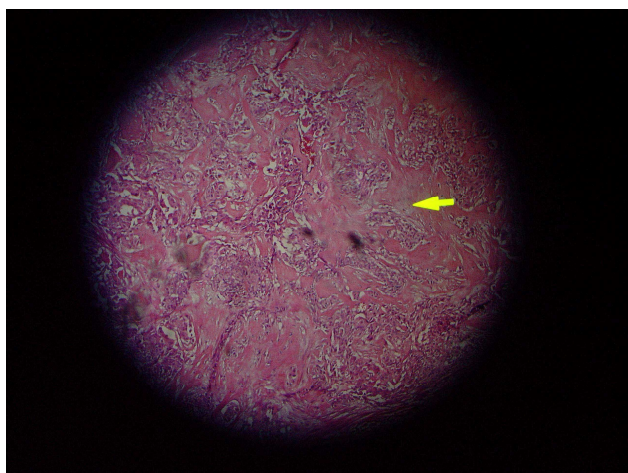


Figure 5. Nesting pattern of the neoplasm with the amorphous material deposition in lymph node ($\times 100$)

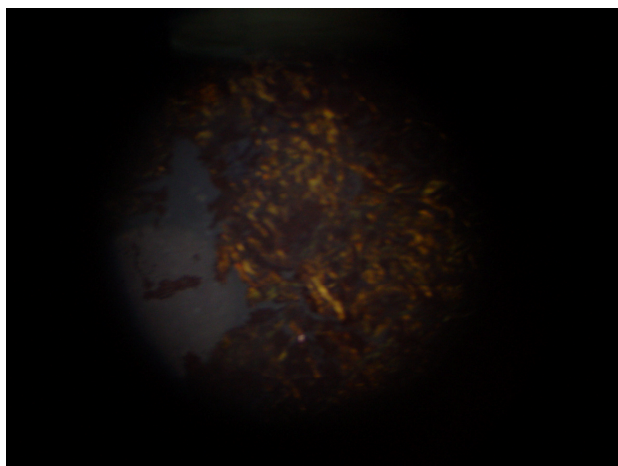


Figure 6. Positive Congo red staining in the lymph node (Polarized lens)

Discussion

We report the case of a patient with metastatic thyroid medullary carcinoma who presented with a positive focus in somatostatin receptor whole body scan during follow-up reevaluation.

This focus corresponded to a mediastinal lymph node metastasis from MTC, as proven by pathology following surgical extirpation of the lesion.

After total thyroidectomy, conventional radiographic modalities such as ultrasound, CT, MRI and ^{99m}Tc -DMSA(V) whole body scan were used for detecting the recurrence or the residue of the tumor, but metastatic lesion escaped detection by these modalities. In this

case report of recurrent MTC, we used ^{99m}Tc -HYNIC-TOC scan and SPECT for detection of the site of the residue. The present report offers potential novel approach in the diagnosis and follow-up of the metastatic medullary thyroid carcinoma.

Endocrine tumors trigger the expression of the receptors, which help us their detection, using nuclear imaging. For example, there are somatostatin receptors types II and III on the surface of the neuroendocrine tumors; Diethylene-triamine-pentaacetic acid (DTPA) - pentetate or HYNIC-TOC in octroskan binds to these receptors and ^{131}I and ^{123}I -meta-iodobenzylguanidine (MIBG) can localize chromaffin cells because these cells express neuropeptide receptors and MIBG binds to them.¹⁸ For localization of the recurrence or residue of the MTC, various scintigraphic methods are used with the radio-labeled molecule such as ^{99m}Tc -sestamibi, ^{99m}Tc -DMSA (V), ^{131}I , ^{123}I -MIBG, ^{111}In -DTPA-pentetate, ^{18}F -flourodexoyglucose (FDG-PET) and radio labeled anti-CEA.¹⁹ None of the above has enough sensitivity and specificity for the definite diagnosis. For example, sensitivity of ^{99m}Tc -DMSA (V), ^{131}I or ^{123}I -MIBG, ^{111}In -Octreotide, ^{99m}Tc -HYNIC-TOC, ^{131}I -anti CEA and FDG-PET in detection of MTC recurrence or metastasis is 70%, 30%, 65%, 80%, 78% and 73%, respectively.²⁰

Parisella et al described five cases of MTC with hypercalcitoninaemia several years after thyroidectomy. In all the patients, scintigraphy with ^{99m}Tc -HYNIC-TOC showed tracer uptake in metastatic lymph nodes.²¹

Decristoforo et al and Gabriel et al found that ^{99m}Tc -HYNIC-TOC scintigraphy provided superior scans and higher tumour/background ratios than ^{111}In -DTPA-octreotide.^{22,23}

These results were compatible with our findings.

Conclusion

^{99m}Tc -HYNIC-TOC is useful for scintigraphy in the follow up of patients with MTC. It can

be used in clinical practice for preoperative evaluation, for localization of local recurrence

or distant metastases and particularly for therapy decision making.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

All the authors have carried out the study, participated in the design of the study and writing the manuscript draft. All authors read and approved the final manuscript.

References

1. Mazzaferri EL. Thyroid carcinoma: papillary and follicular. In: Mazzaferri EL, Samaan N, Editors. *Endocrine tumors*. Cambridge: Blackwell Scientific Publications; 1993. p. 278-333.
2. Saad MF, Ordonez NG, Rashid RK, Guido JJ, Hill Cs Jr, Hickey RC, et al. Medullary carcinoma of the thyroid. A study of the clinical features and prognostic factors in 191 patients. *Medicine (Baltimore)* 1984; 63(6): 319-42.
3. Ismailov SI, Piulatova NR. Postoperative calcitonin study in medullary thyroid carcinoma. *Endocr Relat Cancer* 2004; 11(2): 357-63.
4. Moley JF, Debenedetti MK, Dilley WG, Tisell LE, Wells SA. Surgical management of patients with persistent or recurrent medullary thyroid cancer. *J Intern Med* 1998; 243(6): 521-6.
5. Evans DB, Fleming JB, Lee JE, Cote G, Gagel RF. The surgical treatment of medullary thyroid carcinoma. *Semin Surg Oncol* 1999; 16(1): 50-63.
6. Rufini V, Salvatori M, Garganese MC, Di Giuda D, Lodovica Maussier M, Troncone L. Role of nuclear medicine in the diagnosis and therapy of medullary thyroid carcinoma. *Rays* 2000; 25(2) 273-82.
7. Udelsman R, Ball D, Baylin SB, Wong CY, Osterman FA Jr, Sostre S. Preoperative localization of occult medullary carcinoma of the thyroid gland with single-photon emission tomography dimercaptosuccinic acid. *Surgery* 1993; 114(6): 1083-9.
8. Stepanas AV, Samaan NA, Hill CS Jr, Hickey RC. Medullary thyroid carcinoma: importance of serial serum calcitonin measurements. *Cancer* 1979; 43(3): 825-37.
9. Callender DL, Sherman SI, Gagel RF, Burgess MA, Goepfert H. In: Meyers EN, Suen JY, Editors. *Cancer of the thyroid*. *Cancer of the head and neck*. 3rd ed. Philadelphia: WB Saunders; 1996. p. 485-515.
10. Martins RG, Rajendran JG, Capell P, Byrd DR, Mankoff DA. Medullary thyroid cancer: options for systemic therapy of metastatic disease? *J Clin Oncol* 2006; 24(11): 1653-5.
11. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004; 64(19): 7099-109.
12. Carlomagno F, Vitagliano D, Guida T, Ciardello F, Tortora G, Vecchio G, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Res* 2002; 62(24): 7284-90.
13. Ball DW. Medullary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am* 2007; 36(3): 823-37.
14. viii. Schott M, Seissler J, Lettmann M, Fouxon V, Scherbaum WA, Feldkamp J. Immunotherapy for medullary thyroid carcinoma by dendritic cell vaccination. *J Clin Endocrinol Metab* 2001; 86(10): 4965-9.
15. Shikare S, Bashir K, Menon PS, Bapat RD, Tilve GH. Detection of medullary carcinoma of thyroid, with liver metastasis, using [99mTc-DMSA (V)] scintigraphy. *J Postgrad Med* 1995; 41(1): 12-3.
16. Reubi JC, Landolt AM. High density of somatostatin receptors in pituitary tumors from acromegalic patients. *J Clin Endocrinol Metab* 1984; 59(6): 1148-51.
17. American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid* 2009; 19(6): 565-612.
18. Lewington VJ, Clarke SE. Isotopic evaluation and therapy in patients with malignant endocrine disease. *Best Pract Res Clin Endocrinol Metab* 2001; 15(2): 225-39.
19. Behr TM, Gotthardt M, Barth A, Béhé M. Imaging tumors with peptidebase radioligands. *Q J Nucl Med* 2001; 45(2): 189-200.

20. Czepczyński R, Parisella MG, Kosowicz J, Mikołajczak R, Ziemnicka K, Gryczyńska M, et al. Somatostatin receptor scintigraphy using ^{99m}Tc -EDDA/HYNIC-TOC in patients with medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 2007; 34(10): 1635-45.
21. Parisella M, D'Alessandria C, van de Bossche B, Chianelli M, Ronga G, Papini E, et al. ^{99m}Tc -EDDA/HYNIC-TOC in the management of medullary thyroid carcinoma. *Cancer Biother Radiopharm* 2004; 19(2): 211-7.
22. Decristoforo C, Mather SJ, Cholewinski W, Donnemiller E, Riccabona G, Moncayo R. ^{99m}Tc -EDDA/HYNIC-TOC: a new ^{99m}Tc -labelled radiopharmaceutical for imaging somatostatin receptor-positive tumours; first clinical results and intra-patient comparison with ^{111}In -labelled octreotide derivatives. *Eur J Nucl Med* 2000; 27(9): 1318-25.
23. Gabriel M, Decristoforo C, Donnemiller E, Ulmer H, Wafah Rychlinski C, Mather SJ, et al. An inpatient comparison of ^{99m}Tc -EDDA/HYNIC-TOC with ^{111}In -DTPAoctreotide for diagnosis of somatostatin receptor-expressing tumors. *J Nucl Med* 2003; 44(5): 708-16.