



# Case Report and Literature Review of Medullary Thyroid Carcinoma

Rodrigo Arrangoiz\*, Fernando Cordera, David Caba, Manuel Munoz, Eduardo Moreno and Enrique Luque de Leon

Department of Surgery, Sociedad Quirurgica S.C. at the American British Cowdray Medical Center, Mexico

## Abstract

Medullary Thyroid Carcinoma (MTC) accounts for approximately 1.7% of all thyroid malignancies. The majority of MTC are sporadic, but 15% to 25% of the cases result from a germline mutation in the RET proto-oncogene. Surgery is the first-line treatment modality for any patient presenting with respectable MTC. The propensity of MTC to metastasize to regional lymph nodes in the central and lateral compartments of the neck is a defining characteristic of this disease, which explains the surgical management in all clinical settings. Elimination of involved nodes can result in long-term cure or disease control, and a working knowledge of cervical lymph node anatomy and of the natural history of MTC spread within these nodal groups is important to the surgeon managing these patients. The degree and timing of the surgery are discussed centered on evidence-based medicine this case report and literature review discusses the contemporary management approach used for the evaluation, diagnosis and treatment of our patient with MTC.

## Introduction

Medullary Thyroid Carcinoma (MTC) arises from the thyroid parafollicular cells or C-cells, which produce calcitonin, and accounts for 1.7% of all thyroid cancers in the United States [1,2]. Most tumors are sporadic (75% to 80% of the cases) but may occur as a part of the familial syndromes Multiple Endocrine Neoplasia (MEN) 2A, MEN2B, and familial MTC in 20% to 25% of the cases [1]. Surgery is the mainstay of treatment of these tumors, though recent advances in molecular genetics have enabled the development and use of targeted therapies such as tyrosine kinase inhibitors to treat patients with symptomatic metastatic disease [3].

## Case Report

A 44-year old white female with a history of breast cancer during her routine follow-up was found to have an elevated Carcinoembryogenic Antigen (CEA) (444 ng/dl). Upper and lower endoscopies were performed and were found to be within normal limits. A PET/CT was performed, and a right thyroid lobe metabolically active focal uptake was identified with metabolically active lymphadenopathy in the bilateral central compartments and bilateral lateral compartments. Calcitonin levels were obtained and were found to be greater than 7500 pg/dl. An FNA of the thyroid nodule and two lymph nodes in the lateral compartments confirmed the diagnosis of a medullary thyroid carcinoma (Figure 1). Immunohistochemistry was positive for calcitonin, chromogranin, TTF-1, and negative for Gata-3, Ck20, GCDFP-15, MUC-5, CA-19, and tiroglobulina.

During initial staging CT scans of the neck, chest, abdomen (three phase livers protocol) and pelvis were performed identifying extensive lymphadenopathy (largest lymph node measured 3.3 cm × 2.3 cm × 2.1 cm) in the neck and upper mediastinum (level VII) but no metastatic disease. Direct laryngoscopy identified a paretic right vocal cord but clinical changes in the voice were not apparent to the patient or her family. Pheochromocytoma and primary hyperparathyroidism were rule out with the appropriate preoperative tests.

She underwent a total thyroidectomy with intra operative monitoring of the recurrent laryngeal nerve, bilateral central compartment dissections (levels VI and VII) with intra operative recurrent laryngeal nerve monitoring, and bilateral type III modified radical neck dissections, and auto transplantation of the right and left inferior parathyroid gland in the non-dominant left forearm (brachioradialis muscle) (Figure 2,3 and 4).

Final pathology report showed a medullary thyroid carcinoma 4.0 cm × 3.0 cm × 2.8 cm without capsular extension, margins were negative, no lymphovascular invasion and no perineural

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### \*Correspondence:

Rodrigo Arrangoiz, Department of Surgery, Sociedad Quirurgica S.C. at the American British Cowdray Medical Center, Av. Carlos Graef Fernandez # 154, Consultorio 515, Col. Tlaxala Santa Fe, Delgacion Cuajimalpa, Mexico, Tel: 1103-1600; Fax: 1664-7164;

E-mail: rodrigo.arrangoiz@gmail.com

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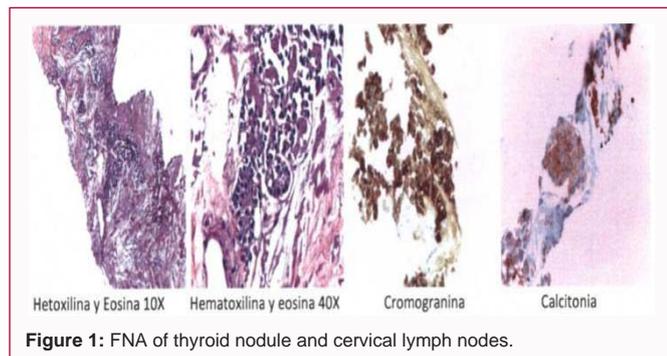


Figure 1: FNA of thyroid nodule and cervical lymph nodes.

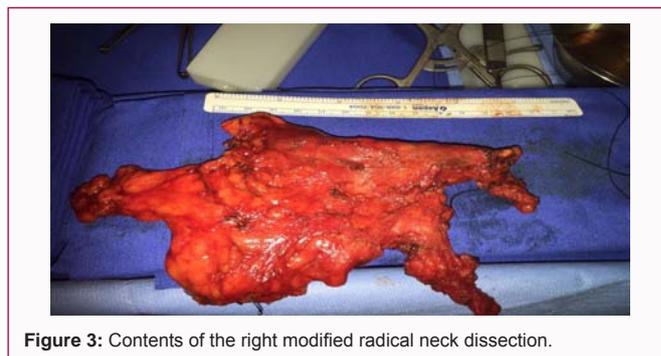


Figure 3: Contents of the right modified radical neck dissection.



Figure 2: Thyroid gland.



Figure 4: Left modified radical neck dissection.

invasion. Central compartment revealed (levels VI and VII) 10 out 12 lymph nodes with metastasis without capsular extension. The lateral compartments showed: right 45/65 positive lymph nodes, left 18/30 positive lymph nodes without nodal extension. Final pathologic staging was a pT3 (s), pN1b, cM0, stage IVA. The postoperative course was uneventful been discharged home on postoperative day number two with levothyroxine, oral calcium and vitamin D supplementation.

The genetic evaluation ordered in the preoperative period came back negative for any RET proto-oncogene mutation. Laboratory evaluation was performed at three-months post-surgery were the calcitonin levels were found to be 369 pg/ml, CEA 22.5 ng/ml, total calcium 8.5 mg/dl, intact PTH 38 pg/ml, and TSH 1.4 mIU/ml. A neck ultrasound, CT of the neck, chest, abdomen (three phase liver protocol CT), pelvis, bone scan, and a MR of the axial skeletal was performed. No structural abnormality was noted, and she was classified as having biochemical incomplete response and she has been followed at six-month intervals. The calcitonin values have been slowly increasing 394 pg/ml, 399 pg/ml, 650 pg/ml, 676 pg/ml, and the CEA levels have also been increasing 22.5 ng/ml, 24 ng/ml, 31 ng/ml, 32.7 ng/ml, 30 ng/ml. During each six-month visit with the rising calcitonin and CEA level a metastatic work-up was performed which included a neck ultrasound, CT of the neck chest, abdomen (three phase liver protocol CT), pelvis, bone scan, and a MR of the axial skeletal, all of them negative for structural recurrence or metastatic disease.

The patient is completely asymptomatic and continuing her strict follow-up knowing that at one point in time she is going to have a structural recurrence or metastatic disease that will require management.

## Discussion

Medullary Thyroid Carcinoma (MTC) accounts for approximately 1.7% of thyroid cancers in the United States [1,2]. These tumors originate from the parafollicular or C-cells of the thyroid gland,

which produce calcitonin as well as other secretory products such as CEA, Adrenocorticotropic Hormone (ACTH), chromogranin, histaminases, neurotensin, somatostatin, and B-melanocyte stimulating hormone [4]. Most MTCs occur sporadically (75% to 80%), but they are also found in hereditary syndromes such as MEN 2A (Sipple syndrome), MEN 2B (Wagenmann-Froboese syndrome) and Familial MTC (FMTC) [1]. MEN2A that accounts for 95% of MEN2 cases is characterized by MTC, Primary Hyperparathyroidism (PHPT), and pheochromocytoma [5,6]. There are four variants of the MEN2A syndrome: classical MEN2A, MEN2A with Cutaneous Lichen Amyloidosis (CLA), and MEN2A with Hirschsprung disease, and FMTC in which the families or individuals have MTC but not pheochromocytomas or Hyperparathyroidism (HPT) [7].

The hereditary forms are characterized by germline mutations in the RET proto-oncogene located on chromosome 10q11.2 [5,7,8]. This oncogene encodes a transmembrane protein receptor kinase and is usually expressed in the cells of the neural crest, branchial arches, and the urogenital system. Approximately 50% of sporadic MTCs harbor RET mutations, and up to 80% of the remaining carry RAS (HRAS, KRAS, or NRAS) mutations [9-11]. All patients with newly diagnosed C cell hyperplasia or apparently sporadic MTC should have germline RET mutation testing (recommendation #21 ATA guidelines) [1,12]. Initial germline testing in patients with C cell hyperplasia or apparently sporadic MTC should include sequencing of exons 10, 11 and 13 through 16 of the RET gene [1,12-14]. Sequencing of the residual exons in the RET gene should be considered in patients with clinical manifestations or family history indicative of hereditary medullary syndromes who express no mutations in exons 10, 11 or 13 through 16 [13]. Our patient had appropriate RET proto-oncogene testing that was negative indicating a sporadic case of MTC. We strongly encourage discussion with genetic counselors that are aware of both the ethical issues and legal informed consent requirements that are involved in germline testing [1,12].

Sporadic MTC typically occurs between the fourth to sixth

decades of life; however, patients with hereditary disease present earlier. Our patient was diagnosed at 44-years of age based on an incidental finding of an elevated CEA level. Patients often have a thyroid nodule, which may be associated with palpable cervical lymphadenopathy (15% to 20% of the cases) [14]. The elevated CEA level in our patient resulted in an extensive work-up that included a PET/CT scan which showed focal uptake in the right thyroid lobe with multiple metabolically active lymph nodes in the central and lateral compartments of the neck. An ultrasound was performed confirming that the focal metabolic uptake seen on the PET/CT was a 4 cm thyroid nodule. Although pain or aching is also a common symptom of MTC our patient was totally asymptomatic. Our patient did not have any symptoms of local tumor invasion such as dysphagia, dyspnea, or dysphonia. Patients with extensive metastatic disease frequently develop diarrhea, which may result from increased intestinal motility and impaired intestinal water and electrolyte flux due to high calcitonin levels [14]. Despite having calcitonin levels greater than 7500 pg/ml our patient did not have diarrhea or flushing. Approximately 2% to 4% of patients develop Cushing syndrome as a result of ectopic production of ACTH.

Fine-Needle Aspiration (FNA) biopsy is used to make the diagnosis of MTC in patients with a solitary thyroid nodule (or a dominant nodule within a multinodular goiter) [14]. The sensitivity of FNA for the diagnosis of MTC is 50% to 80%, though a higher sensitivity can be achieved by adding the immunohistochemical staining for calcitonin [15-17] (Figure 1). When the suspicion for MTC is high (patient with flushing, diarrhea, in the context of a thyroid nodule), calcitonin can be measured in the washout of the FNA biopsy needle [16]. The FNA cytology report often displays discohesive or weakly cohesive cells that may be spindle-shaped, plasmacytoid, or epithelioid in appearance [14,18]. Furthermore, giant cells, oncocytic clear cells, and small carcinoma-like cells may also be present. The nuclei are generally eccentric, and chromatin granularity is seen as a salt and pepper appearance similar to other neuroendocrine tumors [14]. The presence of amyloid is helpful but not by itself diagnostic [19]. The diagnosis is confirmed by immunostaining for calcitonin, chromogranin, or CEA [14]. Thyroglobulin staining is usually negative as is the case with our patient. As it is not possible to distinguish sporadic from familial disease at initial presentation, all new patients with MTC should be screened for RET point mutations, pheochromocytoma, and HPT as was performed in our patient.

Our patient who was diagnosed *via* cytological evaluation the initial work-up that we performed included a complete history and physical examination, measurement of serum calcitonin, CEA, ultrasound of the neck, in selected cases calcitonin in FNA washout, genetic testing for germline RET mutations, and biochemical evaluation for coexisting tumors, especially pheochromocytoma as recommended by the American Thyroid Association and the NCCN guidelines (recommendation #15, 19, 21, 22 ATA guidelines) [1,12].

Preoperative calcitonin levels may correlate with tumor size in both sporadic and familial cases of MTC [20]. Preoperative calcitonin level of cutoff 50 pg/mL may help predict who will have a biochemical complete response after surgery. Cohen et al., reported in their study in which 45 patients who had a preoperative calcitonin level of 50 pg/mL or less, 44 had normal levels after surgery [20]. Compared to only 50 of 120 patients with preoperative calcitonin levels higher than 50 pg/mL had normal concentrations after surgery [20]. Our patient calcitonin decreased from more than 7500 pg/ml to 366 pg/ml but

never achieved a complete biochemical response. Machens et al., [21] reported that 62% of the patients with MTC without nodal metastases had normal calcitonin postoperatively, while 10% of patients with nodal metastasis had normal postoperative calcitonin levels.

Contrast-enhanced CT of the neck and chest, three-phase contrast-enhanced multi-detector liver CT, or contrast-enhanced MRI of the liver, and axial MRI and bone scintigraphy are recommended in patients with extensive neck disease and signs or symptoms of regional or distant metastases, and in all patients with a serum calcitonin greater than 500 pg/mL (recommendation #22 ATA guidelines) [1]. FDG-PET/CT nor F-DOPA-PET/CT is recommended to detect the presence of distant metastases (recommendation #23 ATA guidelines) [5].

The North American Neuroendocrine Tumor Society, the ATA, and the National Comprehensive Cancer Network (NCCN), have published guidelines for the management of patients with both sporadic and hereditary MTC [1,12,22]. MTC can only be cured by complete resection of the thyroid tumor and any local and regional metastases [1,12]. Total thyroidectomy is the treatment of choice for patients with MTC because of the high incidence of multicentricity, the more aggressive course compared with differentiated thyroid cancer, and the fact that 131I therapy is usually not effective [1,12,14]. For MTC limited to the neck and no evidence of involved cervical lymph nodes on preoperative ultrasound, total thyroidectomy with prophylactic bilateral central compartment lymph node dissection is the desired initial treatment (recommendation #24 ATA guidelines) and this was the recommended management that we offered our patient [1,12]. Roughly 10% of patients with sporadic MTC and all patients with familial MTC have bilateral or multifocal disease; likewise, the latter all have premalignant diffuse C cell hyperplasia [1]. Therefore, total thyroidectomy rather than unilateral lobectomy is the preferred surgical approach [1].

MTC patients with unilateral intrathyroidal tumors are reported to have lymph node metastases in 81% of central compartment (level VI) dissections, 81% of ipsilateral lateral compartment (levels II to V) dissections, and 44% of contralateral lateral compartment (levels II to V) dissections [23]. Very similar numbers are reported for patients with bilateral tumors. Additionally, the incidence of lateral compartment nodal disease depends on the frequency of metastases in the central compartment. Preoperative neck ultrasonography and basal calcitonin/CEA levels may be helpful to define the extent of nodal metastases and hence guide surgery, although this is debatable. Patients with basal calcitonin levels greater than 20 pg/mL are unlikely to have nodal metastases [21]. Increasing calcitonin levels (>20 pg/mL), are associated with metastases to the ipsilateral central and ipsilateral lateral compartment. Contralateral central compartment (>50 pg/mL), contralateral lateral compartment (>200 pg/mL), and upper mediastinum (>500 pg/mL) [1,12,14,21,23]. As such, biochemical cure can be achieved in patients with preoperative calcitonin levels less than 1000 pg/mL but is unlikely in patients with levels greater than 10,000 pg/mL [21]. Our patient had preoperative calcitonin levels greater than 7500 pg/mL, the patient had bilateral central, lateral, and upper mediastinum lymph node metastasis. We performed a complete surgery but could not achieve a complete biochemical response, but this was anticipated based on the work by Machens et al., [21].

The current ATA guidelines recommend that patients without nodal metastases on ultrasonography and no distant disease undergo

a total thyroidectomy and bilateral level VI node dissection [1]. In this scenario, no consensus was reached regarding the optimal management of the lateral compartments, and the guidelines indicate that a prophylactic lateral neck dissection may be considered based on calcitonin levels (recommendation #25 ATA guidelines) [1]. The ATA guidelines could not attain a consensus agreement on this topic but did recommend that prophylactic lateral neck dissections "may be considered based on serum calcitonin levels" (recommendation #25 ATA guidelines) [1]. In contrast, the NCCN guidelines suggest considering a prophylactic ipsilateral modified neck dissection for high-volume or gross disease in the adjacent central compartment if the tumor is greater than or equal to 1 cm in size or the disease is bilateral [1,12]. In patients with diagnosed lymph node metastases (but no distant disease), total thyroidectomy, bilateral level VI dissection, and dissection of levels II to V in the involved compartment are recommended [12]. Prophylactic dissection of the contralateral neck can be considered if the calcitonin level is greater than 200 pg/mL [12].

Some authors have suggested that prophylactic central compartment neck dissection is not required in patients with small intrathyroidal MTCs with a preoperative calcitonin less than 20 pg/mL, as metastatic lymph nodes are exceedingly rare in these circumstances [21]. Patients with MTC limited to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central compartment lymph nodes (level VI), and dissection of the involved lateral neck compartments (levels II to V). When preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is greater than 200 pg/mL (recommendation #26 ATA guidelines) [1].

External Beam Radiation Therapy (EBRT) as adjuvant therapy to the neck and mediastinum is not routinely indicated but should be considered in patients with incompletely resected disease (ATA and NCCN guidelines) and those considered at high risk for locally recurrent disease (ATA guidelines only) [1,12]. This includes patients with microscopic residual disease, the presence of extrathyroidal extension, or extensive lymph node metastases (recommendation #52 ATA guidelines) [1]. The potential benefits must be weighed against the acute and chronic toxicity linked with this treatment modality [14]. EBRT appears to be effective for local tumor control [24,25]. As a general rule patients should no longer be candidates for repeat neck surgery, as the operation becomes more technically challenging after EBRT [14]. If recommended, 60 Gy to 66 Gy is delivered to the thyroid bed over a 6-week period, although higher doses are needed for gross residual disease [1,12,25,26]. Intensity-modulated radiation therapy is recommended for disease adjacent to the spinal cord to reduce toxicity. Our patient was presented in a multidisciplinary tumor board and will reserve this therapeutic modality if structural disease recurrence is identified in the neck as surgery cannot be performed.

Patients in the postoperative period are risk stratified based on their risk of recurrence into low-risk disease and high-risk tumors. Serum calcitonin and CEA levels are measured at three-months after surgery and if undetectable or within the normal range, the NCCN guidelines recommend annual serum calcitonin and CEA testing [12]. However, the ATA guidelines diverge somewhat and recommend measurement at six-month intervals for 1 year and then once yearly,

provided physical examination is also normal [1]. We are performing the ATA recommended follow-up and surveillance strategy.

Patients with elevated calcitonin levels, as our patient was found to have three-months after surgery, need additional imaging [1,12]. If calcitonin is less than 150 pg/mL, ultrasound is recommended and if no disease is identified and the physical examination is unremarkable, these patients can be followed at six-month intervals with examination, labs, and neck ultrasonography [1,12]. If postoperative calcitonin is greater than 150 pg/mL, the patients need evaluation by neck ultrasonography, chest CT, contrast-enhanced MRI, or triple-phase contrast-enhanced CT of the liver, bone scintigraphy, and MRI of the axial skeleton and pelvis to evaluate for metastatic disease (recommendation #48 ATA guidelines) [1,12]. The liver is the most common site of distant metastases in patients with MTC, occurring roughly in 45% of patients with advanced disease [1]. Other sites of distant metastasis include bone, brain, and lung [14]. If imaging work-up is negative, monitoring with history and physical exam, calcitonin and CEA levels, and evaluation of the neck with ultrasonography should continue. Brain imaging is indicated only if patients have neurological symptoms [1,12]. Measurement of calcitonin and CEA doubling times can also be used to determine the rate of progression of MTC [27,28]. A meta-analysis of ten studies confirmed that although both measurements are strong indicators of the risk of recurrent MTC and death, the CEA doubling time has a higher predictive value [29].

The frequency of repeating imaging studies will be dependent on the magnitude and rate of rise of the calcitonin and CEA levels. Patients with stable postoperative calcitonin levels in the 150 pg/mL to 300 pg/mL range are usually followed with yearly neck ultrasound for several years, reserving repeat cross-sectional imaging (neck, chest, abdomen, pelvis) looking for distant metastases in those patients with rising calcitonin or CEA levels as has occurred in our patient with a rise in her calcitonin levels from 399 pg/mL to 650 pg/mL. PET/CT scans are considered only when the calcitonin concentrations are higher than 500 pg/mL to 1000 pg/mL [30]. We will be considering ordering a PET/CT based on the next calcitonin/CEA levels and imaging results in her next surveillance visit. Radionuclide bone scan can be helpful in selected cases when cross-sectional imaging fails to identify the source of the elevated calcitonin levels [31-33]. In our patient the bone scans have been negative up to know.

## Conclusion

MTC is a rare tumor. Surgery remains the first-line strategy for any patient presenting with resectable MTC. The tendency of MTC to metastasize to regional lymph nodes in the neck is a defining characteristic of this disease, which explains the surgical treatment in all clinical settings. Elimination of involved nodes can result in long-term cure or disease control, and a working knowledge of cervical lymph node anatomy and of the natural history of MTC spread within these nodal groups is important to the surgeon managing these patients. Further research is needed to elucidate the role of EBRT in the armamentarium for local control post resection, advanced-stage MTC, and palliation. Ample research is still needed to find efficacious therapies for the treatment of persistent and recurrent unrespectable disease.

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