CLINICAL CASE

Medullary Thyroid Cancer Metastatic to the Oral Cavity: Clinical Case

Luis Cruz-Benítez1,*, Angélica Julián-Castrejón2 and Juan de Dios Pérez-Reyna3

1Department of Surgical Oncology and 2Department of Maxillofacial Surgery, HRAEI, SS, Ixtapaluca, Mexico; 3General Surgery 4th-Year Resident, Hosp. Gral. Dr. Darío Fernández Fierro, ISSSTE, Mexico City, Mexico

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Abstract  Medullary thyroid cancer is a neoplasm of the C cells, the function of which is to regulate calcium metabolism. It has a low incidence rate, accounting for 5% of all thyroid cancers. Its occurrence is usually sporadic (84%) or hereditary (16%), with the latter occurring within the context of familial medullary thyroid cancer or multiple endocrine neoplasia type 2, which is associated with different mutations of the proto-oncogene RET 4. It is characterized by secreting calcitonin, which is a useful marker for staging, residual disease detection, and long-term patient follow-up. It is a relatively aggressive neoplasm since despite its slow progression, 60-80% of cases have lymph node metastases at diagnosis, which hinders fully curative therapy since more than 50% of patients have been observed to maintain elevated calcitonin levels after the first surgery. Patients with the hereditary form tend to be younger and to experience more aggressively evolving disease, with cancer often being multifocal and bilateral. The first line of therapy is surgery. (creativecommons.org/licenses/by-nc-nd/4.0/)

*E-mail for correspondence: crubeluis@gmail.com, crubeluis@yahoo.com.mx (L. Cruz-Benítez)

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INTRODUCTION

A large variety of lesions, either malignant or benign, may cause thyroid nodules. Therefore, any patient with this condition should be investigated with regard to family history of benign or malignant thyroid disease (medullary thyroid cancer, multiple endocrine neoplasia type 2, familial papillary thyroid tumors, polyposis coli, Cowden disease, Gardner syndrome and Carney complex). A thyroid nodule is defined as the presence of one or more focal lesions, either palpable or visible by imaging studies, and that differ from the structure of thyroid parenchyma.

Medullary thyroid carcinoma (MTC) was identified in 1959 by Hazard, et al., who described a variety of solid, non-foveal thyroid cancer, with a stroma rich in amyloid substance and high incidence of lymph node metastases. In 1967, Williams and Brewer described that MTC originates in parafollicular cells (C cells) of the thyroid gland. One year later, Neher demonstrated that this tumor secretes thyrocalcitonin.

Medullary thyroid cancer (MTC) is a neoplasm of calcitonin-producing C cells, the function of which is to regulate calcium metabolism. It has a low incidence rate, accounting for 4-5% of all thyroid cancers. Its occurrence is usually sporadic (84%) or hereditary (16%), with the latter occurring within the context of familial MTC or multiple endocrine neoplasia type 2 (MEN 2), which is associated with different mutations of the RET proto-oncogene. Sometimes, this cancer can spread to the lymph nodes, the lungs, or the liver, even before a thyroid nodule is detected. This type of thyroid cancer is more difficult to discover and treat.

This neoplasm is characterized by secreting calcitonin, which is a useful marker for staging, residual disease detection, and long-term patient follow-up. It is a relative aggressive neoplasm since, despite its slow progression, 60-80% of cases have lymph node metastases at diagnosis, which hinders fully curative therapy since more than 50% of patients have been observed to maintain calcitonin elevated levels after the first surgery.

Patients with the hereditary form tend to be younger and to have forms of the disease with more aggressive evolution, with cancer often being multifocal and bilateral.

There are two types of thyroid cancer:
- Sporadic MTC accounts for approximately eight out of every 10 MTC cases, and is not hereditary. This cancer occurs mainly in older adults and it affects only one thyroid lobe.
- Familial MTC is hereditary, and it can occur to 20-25% of members of each generation of a family. These cancers often develop during childhood or early adulthood and can spread early. Patients usually have cancer at several areas of both lobes. Familial MTC is often associated with an increased risk for other types of tumors. Familial medullary thyroid cancer can be associated with hypercalcemia and adrenal tumors (pheochromocytomas). Familial MTC is part of type 2 MEN, the classification of which is the following:
  - MEN 2A (Sipple’s syndrome): MTC, pheochromocytoma and primary hyperparathyroidism.
  - MEN 2B: MTC, pheochromocytoma, intestinal and mucosal ganglioneuromatosis and marfanoid habitus.

- Familial medullary thyroid carcinoma (FMTC): families with more than 10 mutation carriers, or families with multiple carriers or older than 50 years affected members, after detailed history-taking to rule out other endocrine tumors. Also, according to Eng, et al. classification, families with four or more affected members.
- MEN 2A with lichen amyloidosis.
- MEN 2A or FMTC with Hirschsprung’s disease.

CLINICAL PRESENTATION

Usually, it appears in the form of a palpable thyroid nodule. It can be accompanied by systemic symptoms such as diarrhea and hot flashes, which are more common in patients with large tumors. Metastases to paratracheal and lateral cervical lymph nodes occur early in 20-30% of tumors < 1 cm, in 50% of tumors between 1 and 4 cm, and in up to 90% of tumors > 4 cm or T4. Rapidly growing tumors can occur with local invasion symptoms (dysphonia, dysphagia and dyspnea) in 15% of cases.

Between 5 and 10% of cases present with distant metastasis to the lung, liver, bone and, less frequently, to the skin and central nervous system. Distant metastases are the main cause of death, and in half the cases they are already present at diagnosis. Lung metastases are macro- or micronodular, generally diffuse and bilateral. Bone metastases are osteolytic or osteoblastic lesions, with increased uptake on scintigram. Liver metastases appear as hyperechogenic images on echography; if they are small, they can be mistaken for liver hemangiomas.

DIAGNOSIS

Genetic tests should be applied to all individuals diagnosed with medullary thyroid cancer. Genetic testing is considered the standard of care, not a research test. If it has been established that the patient has medullary thyroid cancer, the members of his/her immediate family should be examined to determine if there are genetic factors able to predict the development of MTC. Tests are focused on the RET proto-oncogene. In individuals with these genetic alterations, including children and infants, surgical removal of the thyroid gland before cancer has the chance to develop is highly likely to be a preventive cure. Nearly 100% of patients with the mutation (an abnormal sequence in the RET proto-oncogene) will eventually develop MTC. This specific mutation is useful to determine if the thyroid gland must be extirpated or not.

The RET (REarranged during Transfection) proto-oncogene is found in chromosome 10q11.2, and it contains 12 exons. It encodes for a membrane receptor with tyrosine kinase activity. It is expressed in neural crest-derived cells: C cells, parathyroid cells, chromaffin cells of the adrenal medulla, enteric autonomic plexus and genitourinary tract.

Medullary thyroid cancers normally produce calcitonin and carcenobryonic antigen (CEA), which can be measured with blood tests. Calcitonin (CT) is a 32-amino acid peptide, which is encoded in chromosome 11. It is the main tumor marker in MTC, and it shows high sensitivity and specificity. It is used for initial screening and postoperative follow-up.
Its levels are also increased in neonates, at pregnancy and breastfeeding, in kidney failure, thyroiditis, follicular tumors, C-cell hyperplasia (CCH) and in pancreas and respiratory tract endocrine tumors. With lower sensitivity and specificity than calcitonin, the carcinoembryonic antigen (CEA) is useful for follow-up.

Medullary thyroid cancer is unable to absorb iodine; therefore, radioactive iodine (RAI) should not be used in the treatment of MTC. Several studies have demonstrated that MTC shows a high rate of locoregional involvement at diagnosis, which is one of the main problems faced by these patients, since it allows for persistent disease and/or relapse to develop.

TREATMENT

Surgery is the first line of treatment.

Primary treatment: total thyroidectomy and resection of all neoplastic tissue present in the neck. It is practiced in:

- Patients with no clinical/imaging evidence of lymph node metastases: central compartment prophylactic resection (level VI).
- Suspected metastases limited to the central compartment: level VI resection; some endorse prophylactic lateral dissection.
- Central and lateral involvement by pre-surgical imaging: central and lateral compartment resection (levels IIa, III, IV and V).
- In case of distant metastasis or locally advanced disease, a less aggressive surgery can be performed in order to preserve swallowing, speech, and parathyroid function.

TREATMENT OF HEREDITARY MEDULLARY THYROID CANCER

In the presence of pheochromocytoma: first, adrenal surgery. Identify the four parathyroid glands (staining with methylene blue). If they are normal-looking, they can be left or be implanted in a muscle.

In the presence of hyperparathyroidism:

- If there is evidence of adenoma, it is dissected and the remaining ones are transplanted.
- If diffuse hyperplasia is observed, resection of 3½ glands and autologous transplantation of the remnant to the non-dominant forearm.

Long-term prognosis is not as positive as in well-differentiated thyroid cancers. However, clinical trials have been carried out in recent years where new promising drugs have been tested for the treatment of progressive medullary thyroid cancer. One of these drugs is vandetanib (Caprelsa), which has been approved by the US Food and Drug Administration (FDA) for selected patients with medullary thyroid cancer.

MEDULLARY THYROID CARCINOMA METASTASIS TO THE ORAL CAVITY

Oral cancer accounts for approximately 8% of all malignant tumors, out of which 99% are carcinomas, with the most common being tongue (27%), gum (17%), salivary glands (16%), and mouth floor (13%) carcinomas; the remaining 27% correspond to other sites. The male gender is most affected at a 2:1 ratio. It occurs almost invariably in patients older than 40 years. Metastases affecting the oral cavity account for 1% of malignant tumor lesions, and in 30% it is the first manifestation of a malignant tumor that has remained occult and asymptomatic. Clinically, they appear to be benign or reactive lesions of the oral cavity. The bony component is more affected with regard to soft tissues, especially the mandible at the level of premolars and molars, probably because this is a highly vascularized area and because it contains hematopoietic tissue with higher activity.

It is important to mention that nearly 50% of the medullary cancers have lymph node metastases at diagnosis and that 17.5% also have distant metastases. Metastases to the oral cavity must be locally treated to avoid an ulcerated and painful lesion, to facilitate mastication, and to prevent local deformation. Treatment will be individual in each particular case, bearing in mind that if these lesions are removed by surgical treatment alone, the likelihood of relapse is high.

CASE PRESENTATION

This is the case of a 48-year-old female patient who worked as a janitor. She denied chronic-degenerative conditions as well as previous history of allergy, trauma, or surgical procedures. She was assessed at the oncology and maxillofacial surgery departments where she attended due to a three-month history of an oral region mass enlargement with bleeding, which caused discomfort and bleeding during mastication, as well as a one-year history of a mass in the neck with left predominance and progressive growth. The patient referred dyspnea and occasional pain, dysphagia for solids, and adynamia. The following was detected on physical examination: in the oral cavity, a friable, ulcerated lesion, bleeding on palpation, with granulomatous appearance, of approximately 6 x 6 cm in size was observed in the retromolar trigone, compromising the mobility of the left superior or first and second molars (Fig. 1); neck with multiple 1.5 cm...
MTC metastatic to oral cavity

level IIA and IIIA adenopathies on the left side, as well as a bilateral neck tumor with left predominance, of 15 x 4 cm, firm consistency, partially fixed on the left side, with right side tumor, of 6 x 4 cm in size, hard consistency, partially fixed. A biopsy of the right maxilla tumor on August 28, 2015 reported maxillary region squamous cell cancer.

A surgical preparation protocol was started for the performance of the oral cavity tumor resection, as well as for neck tumorectomy. The chest radiograph did not show metastatic-appearing lesions. Facial skeleton and neck CT angiography reported a hypodense lesion in the single phase at the level of the right maxilla, which caused bone and pterygoid apophysis base erosion, measured approximately 4.0 x 3.7 x 3.2 cm on its largest axes, and showed enhancement after contrast medium IV administration; thyroid gland dimensions augmentation driven by a left lobe-dependent heterogeneous nodule that showed enhancement on the periphery, measured 8.6 x 6.1 x 6.1 cm on its largest axes, and caused the airway to shift to the right (Figs. 2 and 3). Thyroid profile: TSH: 2.71 mIU/l, total T3 (tri-iodothyronine): 1.59 ng/ml, free T3: 3.38 pg/ml, total T4 (thyroxin): 6.56 µg/dl, free T4: 0.78 ng/dl, parathyroid hormone: 25.2 pg/ml.

The patient underwent excisional biopsy with right maxillary region involved tooth (Fig. 4), as well as left hemithyroidectomy with the following results: left thyroid tumor, highly vascularized, with infiltration to adjacent tissues, of 10 x 6 x 5 cm in dimension (Fig. 5) and soft consistency; right thyroid was normal. The dissected hemithyroid specimen transoperative study reported follicular tumor vs. thyroid adenoma. Right hemithyroid and left inferior parathyroid gland were then resected, with recurrent laryngeal nerves being respected (Fig. 6). The surgical procedure concluded with no incidents or complications; bleeding: 300 ml. The patient had an adequate postoperative clinical evolution, with slight dysphonia, tolerance to the oral route, neck drainage with scarce serohematic output, and discharge to her domicile was therefore decided.

Subsequently, the definitive anatomopathological diagnosis was established, with the following report: left thyroid lobe with medullary thyroid carcinoma; size: 6.7 x 5.2 x 4.9 cm, surgical margins negative for neoplastic cells, with data of vascular and perineural invasion, without extra-thyroidal extension. Right thyroid lobe free of medullary carcinoma, with data consistent with classic papillary micro-carcinoma, of size 0.5 cm, negative surgical margins, without vascular, perineural or extra-thyroidal invasion. The right maxillary lesion biopsy report indicated metastatic medullary carcinoma.

This diagnosis prompted the performance of a type III modified radical bilateral neck dissection, with the following findings being observed: 1 cm bilateral adenopathies on both sides of the neck, level III. The histopathology report referred: left-side neck lymphadenectomy with 15 lymph nodes without evidence of malignancy; left-side neck lymphadenectomy with nine malignancy free, inactive lymph nodes. A malignancy free parathyroid gland was identified. With these results, staging was: left medullary thyroid cancer, clinical stage IV (T3, N0, M1) and right micropapillary thyroid cancer, clinical stage I (T1a, N0, M0).

She was then assessed by the radio-oncology department, and the decision was made to administer adjuvant conformational radiotherapy to the neck with surgical bed area and oral cavity included, as well as jugular chains, at a dose of 68 Gy to the primary site in 34 fractions, which was completed without complications.

The patient is currently on treatment with levothyroxine 100 mcg/day, with slight dysphonia and tolerance to the oral route. On physical examination, no data consistent with clinical or radiological tumor recurrence were observed three months after treatment conclusion.
DISCUSSION

Medullary thyroid cancer is a low-frequency and locally aggressive evolution malignancy, with an intermediate prognosis between differentiated and anaplastic cancers. However, these patients have been observed to achieve elevated long-term survival rates of 50-85% at 15 years of follow-up. Hence, we can envisage that adequately treating patients with hereditary MTC constitutes a huge challenge, especially within the context of MEN.

Available treatment approaches include the following. Surgery is regarded as the only curative treatment. In patients with residual or recurrent disease or distant metastasis, external beam radiation therapy (adjuvant or palliative) can be indicated in selected cases. There is also systemic chemotherapy, but it has very limited efficacy, with partial response only in 10-20% of cases (dacarbazine, 5-fluorouracil and doxorubicin). The presence of RET gene-activating mutations make it an alternative for future treatments targeting its inhibition and, therefore, this approach represents a possibility to improve progression-free survival of these patients.

CT and CEA doubling time (DT) is significantly correlated with disease progression and is an important predictive factor for survival. In those patients with baseline detectable CT and no evidence of disease, CT and CEA should be determined at baseline and every six months to estimate DT. Based on the above, the following was concluded:
- When CT DT was < 6 months, 5- and 10-year survival rate was 25 and 8%, respectively;
- If CT DT was between 6-24 months, 5- and 10-year survival was 92 and 37%, in that order;
- In patients with CT DT > 2 years, five-year survival was 100%.

With regard to prognosis, 90% of patients with hereditary medullary thyroid cancer detected early by screening remain disease-free. According to the TNM classification, the 10-year survival rate for stages I, II, III and IV is 100, 93, 71, and 21%, respectively. Conversely, survival with distant metastasis is estimated to be 51% at one year, 26% at five years and 10% at 10 years. Poor prognostic factors include disease stage and old age at diagnosis. In multivariate analysis models, only stage and patient age at initial treatment are significant and independent indicators of survival.

CONCLUSION

Metastatic medullary thyroid cancer has poor responses to radiotherapy and chemotherapy, and adequate screening and the possibility of early surgery are therefore essential in individuals at risk. In this regard, plasma calcitonin measurement in all patients with nodular thyroid disease could be proposed. It is important for genetic studies to be performed in all MTC cases in order to rule out associated pathologies. The only curative treatment in MTC is early and complete surgery, which requires an early diagnosis, with an option also being the implementation of an aggressive surgical approach, since medullary thyroid cancer is associated with an elevated rate of persisting disease and relapse. We should not forget that there are new investigational drugs based on molecular oncology as potential treatment for patients with medullary thyroid cancer at advanced stages.
DELLARATION OF INTEREST

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REFERENCES


