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Case Report

Calcitonin-Negative Neuroendocrine Carcinoma of the Thyroid Gland: Case Report and Literature Review

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Keywords
Calcitonin-negative neuroendocrine tumor · Neuroendocrine tumor · Chemotherapy · Cisplatin · Etoposide

Abstract
Calcitonin-negative neuroendocrine tumor (CNNET) of the thyroid is an extremely rare entity. In some of the previously reported cases within the literature, the terms "atypical medullary thyroid carcinoma," "calcitonin-free oat cell carcinoma," and "a distinct clinical entity" were applied to NETs without definitive evidence of calcitonin production. In the English-language literature, not only are there only few reported cases of CNNET, but the criteria for diagnosis in these cases are also controversial. Most of the current published cases were also treated surgically for local disease. We describe a case of NET of the thyroid with calcitonin, chromogranin A and thyroglobulin negativity, synaptophysin and TTF-1 positivity, and a high Ki-67 proliferation index with metastases in the cervical region as well as mediastinal adenopathies. This case was considered an unresectable thyroid carcinoma, and chemotherapy including cisplatin and etoposide was started as neoadjuvant treatment at the department of medical oncology. Total thyroidectomy plus bilateral and central cervical dissection was performed, and the patient underwent 2 cycles of adjuvant radiotherapy. Currently, the patient's ^{18}F-FDG-PET/CT findings show a complete response 17 months after diagnosis. In conclusion, CNNET

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of the thyroid is very rare and there is limited evidence regarding treatment in patients with metastases. Chemotherapy including cisplatin and etoposide as well as early aggressive surgical resection appears to positively impact patients' survival.

Introduction

Neuroendocrine tumors (NETs) originate mostly from neural crest-derived cells and are primarily seen in the stomach, pancreas, intestines, and lungs [1]. Both the 2010 World Health Organization (WHO) nomenclature and the European Neuroendocrine Tumor Society (ENETS) consider all NETs as malignant neoplasms and also classify them by cellular proliferation and degree of differentiation [2].

Neuroendocrine lesions of the thyroid are rare entities. The most important subgroup includes those lesions derived from C cells (C-cell hyperplasia and medullary carcinoma and its variants) [3]. Medullary thyroid carcinoma (MTC) accounts for 5–8% of all thyroid tumors; although most (70–80%) of cases are sporadic, a familial pattern with an autosomal dominant trait is present in 20–30% of cases. Familial medullary carcinoma occurs in multiple endocrine neoplasia syndromes of the type 2 variety [4, 5].

Immunohistochemical positivity for calcitonin (CT) is required for a diagnosis of true MTC. It is the most aggressive well-differentiated thyroid carcinoma, with survival rates of 40–50% at 10 years [6]. Thyroid NETs present as MTC and represent only 1% of all thyroid cells. In the English-language literature, there are just a few reported cases of calcitonin-negative MTC, and the criteria for diagnosis and treatment are controversial. It is important to recognize this pathological entity, since the prognosis and recurrence may differ from those of more common NETs of the thyroid, including MTC [4, 7–11].

We describe one case of NET of the thyroid with calcitonin, chromogranin A and thyroglobulin negativity, synaptophysin and TTF-1 positivity, and a high Ki-67 proliferation index with metastases in the cervical region as well as mediastinal adenopathies.

Case Report

A previously healthy 33-year-old male with no medical comorbidities, a nonsmoker not consuming alcohol or drugs whose family history did not include any endocrine disorders or cancer syndromes and who denied any history of radiation exposure, hoarseness, dysphagia, weight loss, flushing or diarrhea, presented in October 2017 with a palpable thyroid mass in the left cervical region. Physical examination revealed a rhythmic heart rate of 80 bpm, blood pressure at 110/70 mm Hg, oxygen saturation assessed by pulse oximeter at 94% at room air, and a palpable left thyroid mass of approximately 1-cm diameter, which was nonpainful and nonmobile with a soft consistency.

A thyroid profile was requested, with antithyroglobulin antibody at 160 (normal range 0–40) and carcinoembryonic antigen (CEA) at 0.84 ng/mL (range 0–3); thyroid function and calcium levels were both within normal range. Calcitonin, parathyroid hormone, and urine and plasma metanephrines were not measured. On November 17, 2017, ultrasonography-guided fine-needle aspiration (FNA) of the lymph node (levels III and IV) was performed, which highlighted findings suggestive of large-cell lymphoma. Also, thyroid nodule FNA was conducted, showing atypical lymphoid proliferation suggestive of lymphoma (Bethesda VI) with areas indicative of nonconclusive papillary thyroid cancer.

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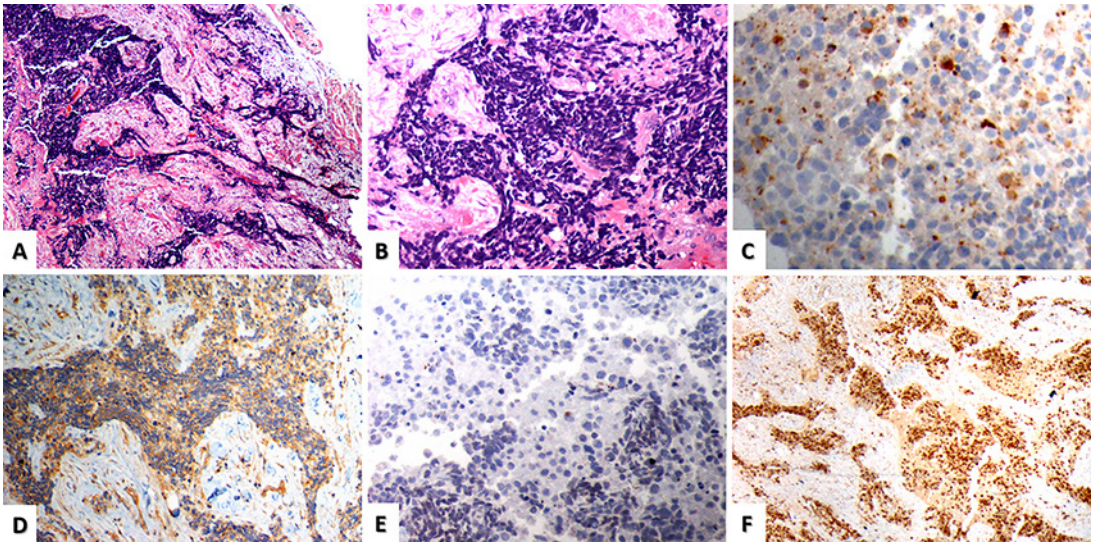

Fig. 1. A Histological section in H&E at low magnification showing a neoplasm with a solid pattern and extensive peritumoral sclerosis. **B** At higher magnification, the cells present of medium size with little cytoplasm and oval hyperchromatic nuclei with granular chromatin. **C–F** Immunohistochemistry was focally positive for synaptophysin (**C**), and diffuse regarding CD56 (**D**) and TTF-1, while calcitonin and chromogranin A (**E**) were negative. **F** The Ki-67 proliferation index was 90%.

On November 24, 2017, lymphadenectomy with thyroid nodule FNA was performed, with the histopathological report of high-grade neuroendocrine carcinoma of the thyroid nodule, negative for calcitonin and metastatic to the lymph node, compatible with a thyroid primary. Immunohistochemical analyses were carried out, which demonstrated to be calcitonin, chromogranin A, CEA and thyroglobulin negative, synaptophysin positive in 30%, CD56 positive in 70%, and TTF-1 positive in 5%; the Ki-67 proliferation index was as high as 90% (Fig. 1).

^{18}F-FDG-PET/CT was conducted on December 2017 outlining a tumor dependent on the left lobe of the thyroid, as well as multiple cervical and mediastinal adenopathies with increased metabolism (Fig. 2A–C). It was confirmed as calcitonin-negative neuroendocrine carcinoma of the thyroid gland, clinical status IVA (T3N1bM0). The patient started chemotherapy on December 12, 2017, with etoposide and cisplatin. He received 6 chemotherapy cycles as neoadjuvant treatment. In March 2018, total thyroidectomy plus bilateral and central cervical dissection was performed. He received 2 cycles of adjuvant radiotherapy. Currently, ^{18}F-FDG-PET/CT showed a complete response 17 months after diagnosis (Fig. 2D).

Discussion and Literature Review

Calcitonin-negative NET (CNNET) is a very rare entity; the current case report would be the 39th report worldwide. NETs arise from the embryonic neural crest, which forms calcitonin-producing C cells, parafollicular cells that migrate and fuse with the primordial thyroid gland. They are present in many organs, especially in the midline organs including the esophagus, stomach, pancreas, intestines, and lungs; less common organs are the thyroid, skin, pituitary, adrenal, and cervix [12, 13].

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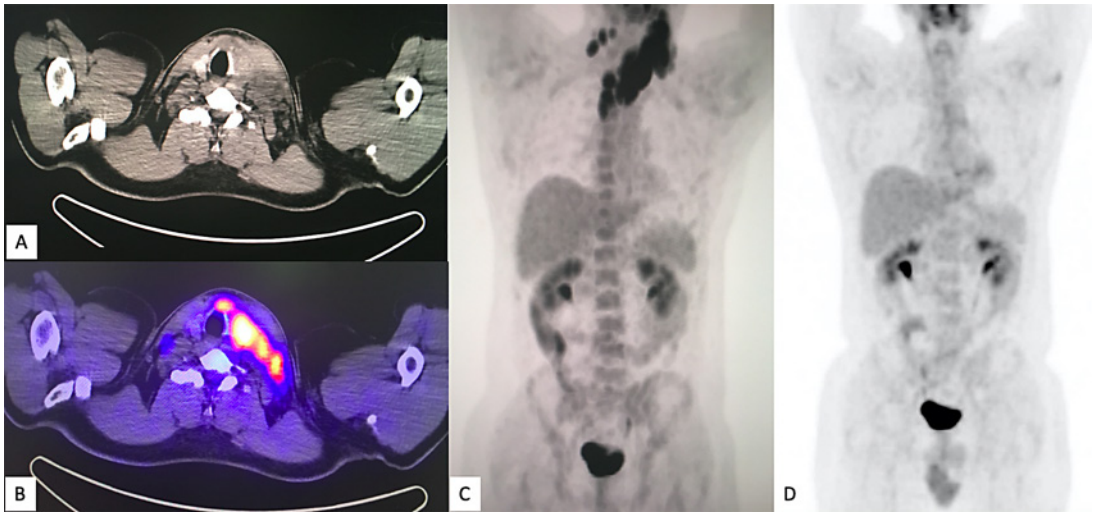

Fig. 2. ^{18}F-FDG-PET/CT. **A–C** Tumor dependent on the left lobe of the thyroid 4.7 × 4 cm in size with an SUV_{max} of 23.7, left cervical lymph nodes in cervical levels II–V, and adenopathies in right cervical levels III and IV, as well as mediastinal adenopathies in the aortopulmonary window and upper and lower paratracheal greater than 15 × 19 mm with an SUV_{max} of 10.4. **D** No evidence of adenopathy or increased metabolism at the site of the previous tumor.

The 2010 WHO nomenclature and ENETS consider all NETs (e.g., gastroenteropancreatic) as malignant and classify them by cellular proliferation and degree of differentiation. Neuroendocrine carcinoma is considered a grade 3 tumor, since it has >20 mitoses/10 high-power fields, has a Ki-67 proliferation index >20%, and could be of the large- or small-cell type [2]. NET of the thyroid is rare; the most common types are MTC and C-cell hyperplasia. Other thyroid nodules and tumors that possess neuroendocrine features include hyalinizing trabecular neoplasms, insular carcinomas, true paragangliomas, parathyroid lesions, and tumors metastatic to the thyroid [3, 14].

The C cells of the thyroid gland secrete several hormones or biogenic amines, including adrenocorticotropic hormone, β-melanocyte-stimulating hormone, calcitonin, CEA, chromogranin, histaminase, neurotensin, and somatostatin. Of these secretory products, calcitonin and CEA are valuable tumor markers in patients with MTC, and their serum concentrations are directly related to the C-cell mass [15].

There have been some reports on thyroid neuroendocrine neoplasms morphologically identical to MTC for which there has been no evidence of calcitonin production. In some of these previously reported cases, the terms "atypical MTC," "calcitonin-free oat cell carcinoma," and "a distinct clinical entity" were applied to NETs without definitive evidence of calcitonin production [1, 16]. Between 1989 and 2017, 23 papers, describing a total of 38 cases of calcitonin-negative MTC or CNNET, were produced, and the criteria for diagnosis and follow-up in these cases are controversial [1, 4, 6–10, 16–31].

The first case in the English-language literature was reported by Sobol et al. [17]. An 82-year-old woman had MTC positive for chromogranin A and synaptophysin, and negative for calcitonin, calcitonin gene-related peptide (CGRP) and thyroglobulin; CEA was weak on immunohistochemistry. Thyroidectomy was performed; her evolution was decending and she had a poor prognosis due to metastases to the skin, liver, and bone.

In 1990, Eusebi et al. [18] used the term "calcitonin-free oat cell carcinoma of thyroid" for 2 cases in a 63-year-old woman and a 73-year-old man. Immunohistochemistry showed chromogranin A and synaptophysin positivity, calcitonin and thyroglobulin negativity, and similar

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morphological features to small-cell carcinoma of the lung. Schmid and Ensinger [16] concluded that calcitonin negativity marked an atypical form of MTC and used the term "atypical MTC."

Afterwards, in 2008, Wang et al. [7] published another case of calcitonin-negative MTC, and they reviewed similar cases. They used the term MTC since the tumor cells were positive for CEA, albeit minimally positive for calcitonin and negative for amyloid deposition by Congo red staining.

The term "calcitonin-negative NET," rather than the term "MTC," was used in 2011 by Chernyavsky et al. [1] for cases when calcitonin immunoreactivity was negative. Recently, Nakazawa et al. [28] used the term "C-cell derived calcitonin free neuroendocrine carcinoma of thyroid." They published a case with similar immunohistochemical features.

All the cases of nonsecretory MTC described so far, as well as our case, were observed just in sporadic MTCs. The biological significance of such features is still not defined. A possible hypothesis is that there could be defects in the mechanism of calcitonin synthesis, and deficient calcitonin production might be related to loss of differentiation, which might be an indicator of poor prognosis [9]. In 36 of 38 patients reported in the literature, most of the variables were reported; 19 (52.8%) were women with a mean age of 53.58 years, 55.6% did not have metastases, 8 (22.2%) had locoregional metastases, and the other 8 distant metastases. Nineteen were negative for mutations, 4 had mutations in *M918T*, 2 in *CGRP*, and 1 in *p.ser649*, with respect to calcitonin. Of the 38 patients, 4 were calcitonin positive, 21 calcitonin negative, and 13 weakly calcitonin positive; 29 were positive for chromogranin and 6 were negative for chromogranin; 15 were positive for synaptophysin; 14 were positive for CEA, 15 negative for CEA, and 3 weakly positive for CEA; 5 were positive for TTF-1 and 2 negative for TTF-1; and 3 were positive for thyroglobulin and 11 negative for thyroglobulin. The duration of follow-up of the patients was up to 12 months; of 36 patients, 12 died and 8 of them were at diagnosis.

Similar to our patient, 8 patients with distant metastases are reported in the literature, of whom 1 patient received cisplatin- and etoposide-based chemotherapy, with negativity for calcitonin, positivity for synaptophysin, negativity for CEA, negativity for thyroglobulin, positivity for chromogranin, and negativity for TTF -1 (unlike the patient in our study), without evidence of tumor recurrence per year. For our patient, left hemithyroidectomy was decided 3 months after chemotherapy, showing no evidence of tumor by pathology; then radiotherapy was initiated, and currently, with adequate evolution, the patient is asymptomatic (Table 1).

Initial Assessment

To exclude MTC in a patient with normal/undetectable calcitonin and well-founded suspicion (i.e., suspicious FNA), washout calcitonin from the FNA (with or without complementary calcitonin immunocytochemistry) as well as serum procalcitonin and CEA should be measured. In addition to neck ultrasound, further imaging investigations should be included in the diagnostic workup in order to detect/exclude distant metastases (i.e., CT, magnetic resonance imaging, bone scan, and PET/CT) [9, 11].

Moreover, as nonsecretory MTCs cannot be detected by serum calcitonin screening, they are more often detected at advanced stages [27]. While it is well accepted that early diagnosis is crucial because complete removal of the tumor is the only curative therapy, there is still no consensus on the optimal postoperative surveillance strategy.

Gene Mutations

Mutations in exons 8, 10, 11, and 13–16 of the *RET* protooncogene as assessed by specific polymerase chain reaction account for about 95% of *RET* mutations in familial MTC. *H-RAS* (codons 12, 13, and 61) and *K-RAS* (codon 61) gene mutations were identified in *RET*-negative sporadic MTC. The V600E (1799T>A) *BRAF* gene mutation is also found within the frame of thyroid tumors [8].

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Table 1. Characteristics of the tumors reported in the different studies, as well as their treatment and outcome

Study [Ref.], year	Patient	Tumor size, cm	Metastasis	Cal	Chr	Syn	CEA	TTF-1	Thyr	Gen	Treatment	Outcome
Kasajima et al. [8], 2016	48 years old, F	2.8 × 1.8	None	–	+	+	+	+	NA	–	Left hemithyroidectomy with lymph node dissection	NA
Nakazawa et al. [28], 2014	76 years old, M	6	None	–	+	+	–	+	–	–	Left thyroidectomy	Free of disease 18 months after surgery
Chernyavsky et al. [1], 2011	40 years old, F	1.9 × 1.5	None	–	+	+	+	NA	+	–	Total thyroidectomy	1 year no clinical evidence of tumor recurrence
Schmid and Ensinger [16], 1998	28 years old, M	Not described	Pulmonary metastases	–	+	+	–	ND	–	CGRP	Total thyroidectomy	Died of disease
	46 years old, M	Not described	None	–	+	+	–	ND	–	CGRP	Total thyroidectomy	Died of disease
	37 years old, M	Not described	None	–	+	+	–	ND	–	–	Total thyroidectomy	Died of disease
	45 years old, F	Not described	None	–	+	+	–	NA	–	–	Total thyroidectomy	9 months after surgery
Sobol et al. [17], 1989	82 years old, F	3	Distant and lymph node metastases	–	+	+	W	NA	–	ND	Total thyroidectomy	Died of disease 23 months after surgery
Eusebi et al. [18], 1990	63 years old, F	7×6.5	Lymph node metastasis	–	+	+	ND	ND	–	ND	Total thyroidectomy	1 month after surgery
	73 years old, M	5	Lymph node metastases	–	+	+	ND	ND	–	ND	None	Died of disease
Wang et al. [7], 2008	68 years old, M	7	Lymph node metastasis	–	+	+	–	+	–	ND	Total thyroidectomy with lymph node dissection	1 year no clinical evidence of tumor recurrence
Ismi et al. [4], 2015	57 years old, M	15×8	Metastases to peritoneum	–	+	+	–	–	–	ND	Chemotherapy with etoposide and cisplatin	NA
Kim et al. [30], 2015	34 years old, M	0.6×0.88	None	–	+	+	–	+	+	ND	Right lobectomy	1 year no clinical evidence of tumor recurrence
Mussazhanova et al. [29], 2014	64 years old, M	5.4×2.7	Lymph node metastasis in superior mediastinum	–	+	+	–	–	+	–	Right thyroidectomy with dissection of lymph nodes	1 year no clinical evidence of tumor recurrence
Parmer et al. [10], 2017	74 years old, F	1.6×1.4	None	–	+	+	+	+	–	ND	Total thyroidectomy	NA
Sand et al. [6], 2006	73 years old, F	3	Lymph node, lung and intracerebral metastases	W	NA	NA	W	NA	NA	NA	Thyroidectomy with dissection	Died 6 weeks after diagnosis
Bockhorn et al. [22], 2004	50 years old, F	2	None	W	+	NA	+	NA	NA	–	Total thyroidectomy, central lymph node dissection	No evidence of disease at 5 years
Redding et al. [21], 2000	31 years old, F	4.5	None	W	–	NA	+	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	No evidence of disease at 30 months
Iglesias et al. [19], 1997	65 years old, F	NA	NA	W	NA	NA	NA	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	Died of disease

Table 1 (continued)

Study [Ref.], year	Patient	Tumor size, cm	Metastasis	Cal	Chr	Syn	CEA	TTF-1	Thyr	Gen	Treatment	Outcome
Giovanella et al. [24], 2008	43 years old, F	4.5	NA	+	+	NA	+	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	No evidence of disease at 2 years
Dora et al. [23], 2008	43 years old, M	1.7	Lymph node metastases	W	+	NA	NA	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	NA
Alapat et al. [25], 2011	16 years old, F	3	None	+	+	NA	+	NA	NA	–	Thyroidectomy	NED at 20 months
Frank-Raue et al. [27], 2013	61 years old, F	1	None	W	+	NA	+	NA	NA	–	Thyroidectomy	NED
	50 years old, F	2	None	W	+	NA	+	NA	NA	Somatic *M918T*	Thyroidectomy	Alive with local recurrence
	47 years old, M	3	Lymph node metastases	+	+	NA	+	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	Alive with local recurrence
	53 years old, F	4.5	Lymph node metastases	W	+	NA	+	NA	NA	Somatic *M918T*	Total thyroidectomy, bilateral lymph node dissection	Died of disease
	70 years old, M	8	Distant and lymph node metastases	W	+	NA	+	NA	NA	–	Total thyroidectomy, bilateral lymph node dissection	Died of disease
	45 years old, M	1.8	Distant and lymph node metastases	W	+	NA	+	NA	NA	Somatic *M918T*	Total thyroidectomy, bilateral lymph node dissection	Alive with local recurrence
	45 years old, F	5.5	Distant and lymph node metastases	W	+	NA	+	NA	NA	Somatic *M918T*	Total thyroidectomy, bilateral lymph node dissection	Died of disease
Brutsaert et al. [31], 2015	39 years old, F	2.6	None	+	+	NA	NA	NA	NA	–	Thyroidectomy	No evidence of disease
Samà et al. [9], 2016	60 years old, M	3.8	None	W	+	NA	W	NA	NA	–	NA	NED at 10 years
	66 years old, F	4	None	NA	NA	NA	NA	NA	NA	–	NA	NED at 10 years
	53 years old, M	1.2	None	–	–	NA	–	NA	NA	*p.ser649Leu*	NA	NED at 3 years
	62 years old, M	4.5	Lymph node mestastases	W	+	NA	–	NA	NA	–	NA	NED at 1 year
Niccoli et al. [20], 1997	68 years old, F	2	NA	–	–	NA	–	NA	NA	NA	NA	NA
	54 years old, M	0.5	NA	–	–	NA	–	NA	NA	NA	NA	NA
Chambon et al. [26], 2011		1	NA	–	–	NA	–	NA	NA	NA	NA	NA
		4	NA	–	–	NA	–	NA	NA	NA	NA	NA

Cal, calcitonin; Chr, chromogranin A; Syn, synaptophysin; Thyr, thyroglobulin; Gen, gene mutations; NA, not available; W, weak; ND, not done; NED, no evidence of disease.

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Immunohistochemistry

Immunohistochemical studies of the colorimetric reaction of the secondary antibody for cytokeratin (CK) AE1/AE3, CK7, CK8, CK18, S100, parathyroid hormone, and Ki-67 must be done. Also assessments of TTF-1, TTF-2 (FOXE1), paired box gene 8 (PAX8), CEA, chromogranin A, synaptophysin, calcitonin, and CGRP must be performed as part of the differential diagnosis [8, 29].

PAX8 and TTF-2 are diffusely expressed in most cases of papillary carcinoma and follicular neoplasms of the thyroid, but their expression in MTC and C-cell hyperplasia varies, being rather indistinct [32].

mRNA in situ Hybridization

It is important to also conduct mRNA in situ hybridization for calcitonin and thyroglobulin. CGRP, expressed both in MTC and in nonneoplastic C cells, is a member of the calcitonin family of neuropeptides which is generated from alternative RNA splicing of the *CALCA* gene. CGRP is also produced in other organs; therefore, CGPR expression alone does not necessarily indicate the origin of the tumor cells. It has been shown to be expressed in at least 2 cases of CNNET of the thyroid [8, 33, 34]. However, together with expression of CK, TTF-1, and PAX8, the presence of CGRP expression is consistent with a C-cell origin [28].

CNNET of the thyroid is extremely rare, and the cells of origin are currently debatable. Some reports have indicated that these tumors originate from thyroid follicular cells based on thyroglobulin immunostaining [1, 30]. Additionally, many reports of CNNETs of the thyroid show contradicting immunostains for thyroglobulin and CEA [28, 29].

Differential Diagnosis

Some other tumors should be considered for a differential diagnosis of calcitonin-nonproducing NETs. In particular, thyroid primary paraganglioma [35], although extremely rare, could be an important differential diagnosis, because its morphology is similar to that of calcitonin-nonproducing NET of the thyroid gland, exemplified by the solid nesting or organoid patterns with capillary vessel networks. Both tumors do not produce calcitonin; however, paraganglioma differs from calcitonin-nonproducing NET in terms of the absence of CK, TTF-1, and thyroglobulin.

Treatment

The main treatment for MTC is surgery, since tumor cells are not sensitive to radioactive iodine uptake. Regarding CNNET, most of the published cases were also treated surgically for local disease. Since our case was metastatic during the diagnosis, chemotherapy was the treatment of choice [4, 5]. Ismi et al. [4] reported a case that was considered an unresectable thyroid carcinoma, and chemotherapy including cisplatin and etoposide was started at the department of medical oncology. After 4 curative chemotherapy regimens, the patient is still followed up at the department of medical oncology. The surgical approach to calcitonin-negative MTC does not differ from the approach to those secreting calcitonin [15].

Follow-Up

Postoperative monitoring for recurrent disease in these patients is difficult. There appears to be no consensus on the optimal imaging technique or method of surveillance. Postoperative follow-up, which is usually tailored to the level and rate of change of calcitonin (i.e., calcitonin doubling time), should include periodical imaging of the neck, chest, and liver, as well as measurement of serum calcitonin, CEA, and procalcitonin in calcitonin-negative MTC. Any increase in serum markers should alert the attending physician, leading to performance of an accurate workup. Patients with a poorly differentiated histological MTC phenotype are

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at higher risk of recurrence and disease-related death; thus, a more aggressive follow-up strategy is recommended in these cases [8, 9].

Although calcitonin-negative MTCs are rare, in patients suspected with MTC, normal/low serum levels of calcitonin and CEA cannot completely rule out the diagnosis [6, 7, 19, 21, 22, 24]. Therefore, routine anatomic imaging is crucial in these patients. Routine imaging studies with neck ultrasound, CT, or magnetic resonance imaging are potentially useful, but they usually fail to detect small lesions. ^{18}F-FDG-PET/CT and ^{18}F-DOPA-PET/CT have been proposed to identify residual tumor masses [36–38], since in different studies they have proved to be superior to conventional imaging procedures in detecting metastases in patients with MTC; in fact, they both showed higher sensitivity in detecting tumor load, and FDG-PET/CT especially seemed to more accurately identify patients with progressive disease [39, 40].

Recently, some authors have suggested following up patients using surveillance imaging including neck ultrasound, chest CT, and CT or magnetic resonance imaging of the liver. Considering bone magnetic resonance imaging of the spine and pelvis as well as bone scanning is also recommended in those patients with symptoms of skeletal involvement [41].

In agreement with other authors, we recommend the evaluation of calcitonin and CEA levels every 6 months in the first year after diagnosis, with a decreasing frequency in the following years, as well as ultrasound of the cervical region, abdominal CT scanning, chest X-ray, and FDG-PET/CT.

Prognosis

Further research is necessary to understand whether CNNET and MTC have the same cells of origin with two different clinical courses and prognoses [10]. The prognosis of calcitonin-nonproducing NET of the thyroid gland remains unclear. For example, MTCs tend to spread to lymph nodes very early and therefore require a more aggressive treatment than other types of differentiated thyroid carcinoma such as papillary and follicular thyroid carcinomas [11]. Early, aggressive surgical resection appears to impact patient survival. Calcitonin is the best indicator for the detection, staging, postoperative management, and prognosis of MTCs [7, 15].

Conclusions

Because CNNET of the thyroid is very rare and there is little evidence regarding treatment of patients with metastases, it is necessary to use an adequate approach. Perform strict follow-up with imaging studies (ultrasound of the cervical region, FDG-PET/CT, etc.) and laboratory studies (calcitonin and CEA) in order to detect recurrence of the disease and its evolution, which may affect its prognosis.

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Statement of Ethics

The patient gave informed written consent to publish this case, including the publication of images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R. Fernández-Ferreira: manuscript redaction, case description, case management, and final writing. I.R. De la Peña-López: manuscript redaction, case description, and case management. K.W. Zamudio-Coronado: analysis and interpretation of the patient data regarding the case, and drafting of the manuscript. L.A. Delgado-Soler: histological examination, analysis, imaging, and redaction of pathology issues regarding the case. M.E. Torres-Pérez: manuscript translation from the original language, information gathering, literature review, and article submission. C. Bourlón-de los Ríos: manuscript redaction, case description, and data analysis. R. Cortés-González: surgical analysis and redaction regarding the case, final writing, and manuscript preparation.

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