

# A Case of Medullary Thyroid Carcinoma Combined with Papillary Microcarcinoma and Literature Review

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## Abstract

**Background:** The histologic type of thyroid carcinomas includes follicular, papillary carcinomas, and medullary carcinomas. The reports about the histological, immunohistochemical, and ultrastructural characteristics of each kind of thyroid carcinomas were common, but the simultaneous occurrence of a medullary and papillary carcinoma as 2 distinct tumors has been reported extremely rarely. **Objects:** To explore the pathogenesis, clinicopathological characteristics, immunohistochemical phenotype, and pathological diagnosis of medullary thyroid carcinoma combined with papillary thyroid microcarcinoma. **Methods:** The clinicopathological characteristics and immunohistochemical phenotype of a patient with left medullary thyroid carcinoma combined with right papillary thyroid microcarcinoma were retrospectively studied. Then, relevant literature was thus reviewed. **Results:** General appearance: The size of the left thyroid lobe was  $2.5 \times 2 \times 1$  cm, the cut surface was gray and red, and a nodule with a diameter of 1.3 cm could be observed. The cut surface of the nodule was gray and yellow, solid, and hard. The size of the right lobe of the thyroid gland was  $0.7 \times 0.6 \times 0.5$  cm, and a gray nodule with a diameter of 0.4 cm was seen on the cut surface. The cut surface of the nodule was gray, solid, and hard. Observation under the microscope: the left nodular tumor cells were round, oval, or plasma cell-like, some areas were arranged in nests, and some areas were arranged in beams. Calcification and sheet-like eosinophilic amyloid deposits could be seen in the stroma. The nodule on the right showed a branched papillary structure, the covering cells on the surface of the nipple were ground glass-like nuclei, and nuclear grooves and pseudo-inclusion bodies in the nucleus could be observed. Immunohistochemistry: left lobe tumor cells Calcitonin, CEA, TTF-1, CD56, CgA, and Syn are all (+), CK19 and TG were both (-); right lobe tumor cells CK19 and TG are both (+), Calcitonin, CD56, CgA, and Syn are all (-). **Conclusions:** The

origin, clinicopathological manifestations, and immunophenotypes of medullary thyroid carcinoma and papillary thyroid carcinoma are different. It is relatively rare for the two to occur at the same time. The diagnosis mainly depends on the microscopic morphology and immunophenotype characteristics.

## Keywords

Thyroid Tumors, Medullary Carcinoma, Papillary Carcinoma, Immunohistochemistry

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## 1. Introduction

Thyroid cancer is the most common tumor in the endocrine system, and its incidence has rapidly increased in recent years. According to differences in origin and differentiation, thyroid cancer is divided into papillary thyroid carcinoma (PTC), thyroid follicular carcinoma (TFC), medullary thyroid carcinoma (MTC), and thyroid cancer. Differentiated carcinoma (anaplastic thyroid carcinoma, ATC) [1]. PTC and MTC tissue origin and clinicopathological manifestations are different, and it is relatively rare for the two to occur at the same time. At present, there are only more than ten cases reported in domestic and foreign literature. There have only been a few reports in the literature describing independent tumors in separate foci in the same thyroid. This article reported the clinicopathological characteristics and immunophenotype of a case of left medullary thyroid carcinoma combined with right papillary thyroid microcarcinoma and discussed its pathogenesis, diagnosis, differential diagnosis, and treatment in combination with the literature, aiming to improve the risk of this type of disease. Awareness level.

## 2. Materials and Methods

### 2.1. Clinical Data

A 44-year-old female patient with thyroid nodules was diagnosed in physical examination. There was no palpitation, shortness of breath, fatigue, no weight loss, excessive eating, no fear of heat, sweating, and facial flushing. There was no swelling in the bilateral thyroid lobe. A nodule with a size of about 1.5 cm × 1.0 cm was palpable in the middle of the left lobe of the thyroid. The texture was hard and smooth. And the boundary was still clear; no obvious nodule was palpable in the right lobe. No tenderness; no swollen lymph nodes were palpable on both sides of the neck. Color Doppler ultrasound of the thyroid and cervical lymph nodes showed that there were 14.3 mm × 7.8 mm × 9.1 mm extremely hypoechoic nodules in the parenchyma of the left thyroid gland, and multiple spot-like strong echo accumulations were seen among them. Several hypoechoic and mixed echo nodules could be observed in the parenchyma of the right lobe,

the maximum size was 5.7 mm × 4.9 mm × 3.7 mm, located in the upper-middle pole, and the boundary was unclear (**Figure 1**, **Figure 2**). Ultrasound prompts: cystic and solid nodules in the thyroid gland in both lobes (multiple on the right), the largest nodules on the right and left nodules TI-RADS grade 4b, and the remaining nodules TI-RADS grade 3. No obvious swollen lymph nodes were seen on both sides of the neck. Serum calcitonin was 761.00 pg/ml. Under general anesthesia, total thyroidectomy + bilateral central lymph node dissection was conducted.

The informed consent was obtained from the patient to report this case.

## 2.2. Methods

The specimens were fixed with 10% neutral formaldehyde, embedded in paraffin, and sections were stained with HE, and observed under a microscope. 4 μm thick serial sections with an automatic, using an automatic immunohistochemistry machine for immunohistochemical detection. All antibodies were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.



**Figure 1.** Color doppler ultrasound of the thyroid and cervical lymph nodes showed that there were 14.3 mm × 7.8 mm × 9.1 mm extremely hypoechoic nodules in the parenchyma of the left thyroid gland.



**Figure 2.** Several hypoechoic and mixed echo nodules could be observed in the parenchyma of the right lobe, the maximum size was 5.7 mm × 4.9 mm × 3.7 mm, located in the upper-middle pole, and the boundary was unclear.

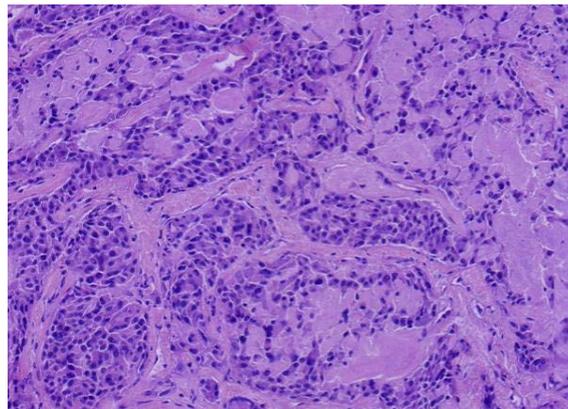
### 3. Results

#### 3.1. General Observation

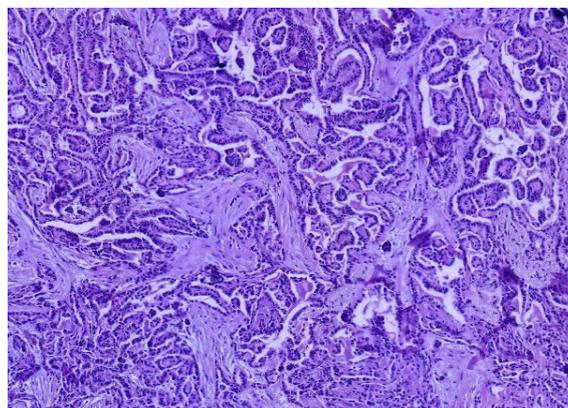
The size of the left thyroid lobe was  $2.5 \times 2 \times 1$  cm, and the cut surface displayed a gray-white nodule with a diameter of 1.3 cm. The cut surface of the nodule was gray-yellow, solid, and hard. The size of the right lobe of the thyroid gland was  $0.7 \times 0.6 \times 0.5$  cm, and a gray nodule with a diameter of 0.4 cm could be observed on the cut surface. The nodule's cut surface was gray, solid, and hard.

#### 3.2. Morphology under the Microscope

The nodular tumor cells on the left are oval, round, or plasmacytoid, some areas were arranged in nests, some areas were arranged in beams, and calcification and eosinophilic amyloid deposits could be seen in the interstitium. The right nodule was about 0.4 cm in diameter and had a branched papillary structure. The covering cells on the surface of the nipple were ground glass-like nuclei, and nuclear grooves and pseudo-inclusion bodies could be discovered (**Figure 3**, **Figure 4**).



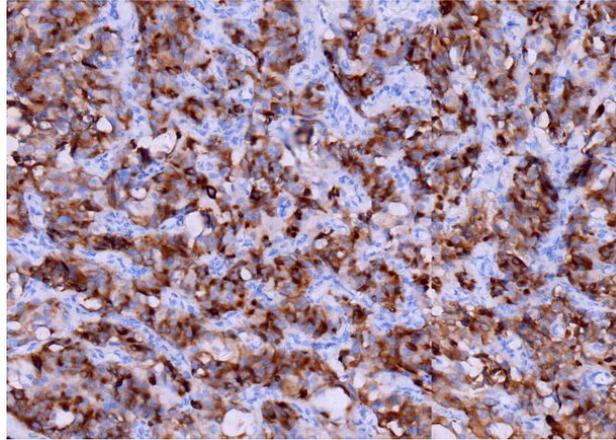
**Figure 3.** The tumor cells on the left side were arranged in sheets and nests, composed of polygonal, round, or spindle-shaped cells, and there was obvious amyloid in the interstitium HE 200 $\times$ .



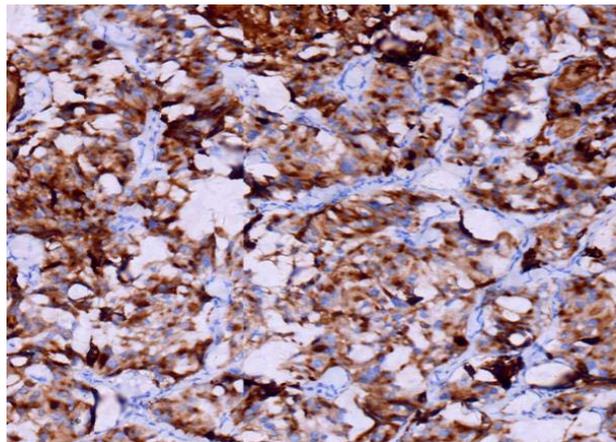
**Figure 4.** The tumor cells on the right side had a branched papillary structure. The arrangement was crowded with ground-glass nuclei HE 200 $\times$ .

### 3.3. Immunohistochemistry Results

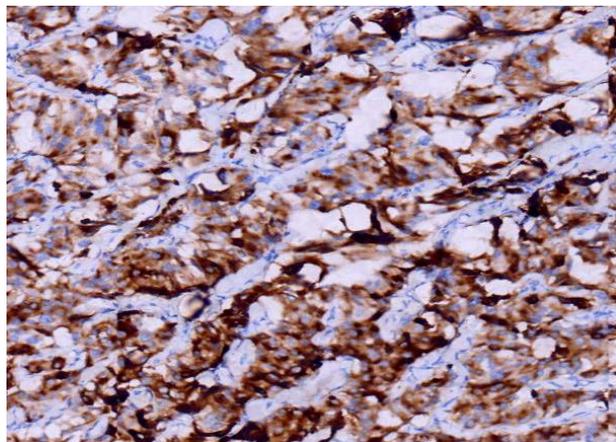
The left lobe tumor cells Calcitonin, CEA, TTF-1, CD56, CgA, and Syn are all (+), CK19 and TG were both (-); the right lobe tumor cells CK19 and TG were both (+), Calcitonin, CD56, CgA, and Syn were both (-) (**Figures 5-10**).



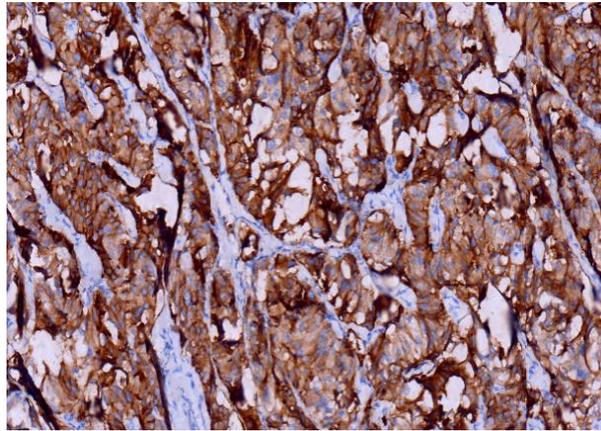
**Figure 5.** Left leaf tumor cell Calcitonin (+) IHC 200 $\times$ .



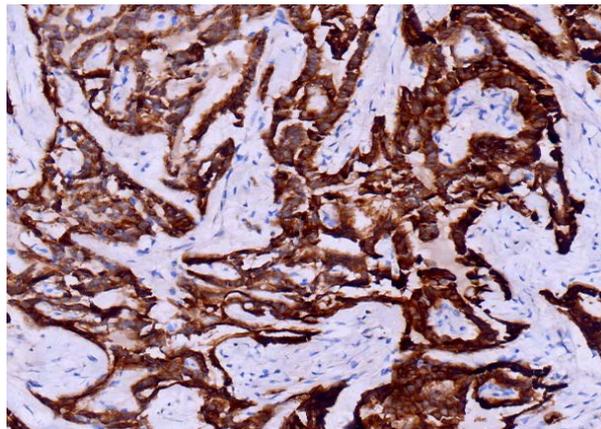
**Figure 6.** Left leaf tumor cell CgA (+) IHC 200 $\times$ .



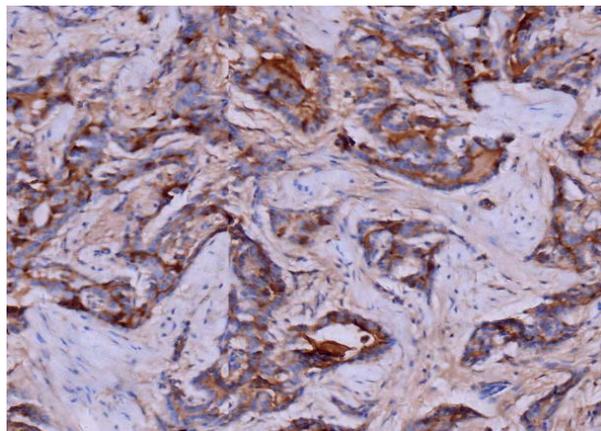
**Figure 7.** Left leaf tumor cell Syn (+) IHC 200 $\times$ .



**Figure 8.** The left leaf tumor cell CEA (+).



**Figure 9.** The right leaf tumor cell CK19 (+) IHC 200 $\times$ .



**Figure 10.** The right leaf tumor cell TG (+) IHC 200 $\times$ .

### 3.4. Pathological Diagnosis

Left medullary thyroid carcinoma, right papillary thyroid microcarcinoma, and no metastatic carcinoma in the central lymph nodes of both sides.

TNM-staging: Left: T1bN0bM0; right: T1aN0bM0.

Post-operation, the patient had a favorable recovery without complications.

After the operation, the patient had no obvious abnormalities at the follow-up consultations in the 11 months.

#### 4. Discussions

MTC is a malignant tumor originating from thyroid C cells (parafollicular cells), accounting for about 1% - 2% of all thyroid cancers [2]. It is divided into sporadic and familial. Sporadic tumors account for about 70% of all medullary cancers and generally occur in 50 - 60 years old, and the familial age of onset is relatively young, occupying around 30%. It is an autosomal dominant genetic disease. Multiple endocrine neoplasia (MEN) type 2, including 2A, 2B, and familial medullary carcinoma, familial medullary carcinoma is considered to be the disease spectrum of MEN2A [3]. PTC is a tumor derived from thyroid follicular epithelium and the most common thyroid cancer, accounting for about 85% - 90% of all thyroid cancers. According to histological characteristics, it is divided into multiple subtypes. Papillary microcarcinoma is one of the subtypes, which refers to papillary thyroid carcinoma with a diameter of less than 1 cm.

Studies have shown that the occurrence and development of thyroid cancer are bound up to BRAF gene mutations, and in PTC, the most representative mutation type is BRAF V600E [4]. The tissue source and molecular mechanism of medullary thyroid carcinoma accompanied by papillary carcinoma are still unclear. At present, scholars at home and abroad mainly hold three opinions: 1) The origin of the same stem cells: that is, they originate from common stem cells and then go to the follicular epithelium of the thyroid. Cells and parafollicular C cells differentiate to form papillary thyroid carcinoma and medullary carcinoma. However, with the deepening of research, Sadat Alavi and Azarpira proposed and confirmed that the two tumors did not originate from the same stem cell. 2) Same proto-oncogene: The occurrence of medullary carcinoma is often caused by the mutation of the RET proto-oncogene. This mutation is inherited in an autosomal dominant manner, but the penetrance is different. Beyond that, about 20% - 40% of PTC also have RET gene rearrangement, but the activation mechanism is different. In MTC, the activation mechanism of RET is usually point mutation or gene deletion and insertion, while chromosome rearrangement is activated. The mechanism can only be found in PTC. Whether this abnormal expression of the RET gene is the mechanism for the simultaneous occurrence of two cancers remains to be studied. 3) Collision tumor: The doctrine believes that the simultaneous occurrence of two types of cancer is just a pure coincidence. In this case, the two cancer foci occurred on both sides and they were independent of each other, which is more inclined to the collision theory.

MTC and PTC are extremely different in terms of tissue origin and clinical manifestations. The simultaneous occurrence of the two is relatively rare, and there are generally no specific clinical and imaging manifestations, usually manifested as thyroid nodules. In this case, the thyroid was accidentally found during physical examination. What's more, it is hard to detect two types of cancer with a preoperative puncture, which can be diagnosed only by intraoperative

freezing. The diagnosis of mixed carcinoma of medullary thyroid carcinoma and papillary carcinoma mainly depends on the microscopic morphology and immunophenotype. The typical manifestations of medullary carcinoma are: tumors are arranged in sheets, nests, and beams, composed of polygonal, round, or spindle-shaped cells, and there are obvious amyloid deposits in the interstitium. The microscopic features of papillary carcinoma are complex branched papillary structures and covered cells with ground glass-like nuclei, and nuclear grooves and nuclear pseudo-inclusion bodies can be seen. The diagnosis can be confirmed by combining their specific immunohistochemical indicators. In this case, because the two types of cancer occurred on different sides of the thyroid, and the microscopic appearance was more typical, it was not hard to conduct the diagnosis. But it was reported in the literature [5] [6] [7] that small focal papillary carcinoma components appear in the background of medullary carcinoma, or small focal medullary carcinoma components appeared in the background of papillary carcinoma. In this case, it was easy to miss the diagnosis, and sufficient materials were required. Under careful observation, the unobvious morphology could be distinguished by immunohistochemistry. The papillary carcinoma area expressed thyroglobulin, while the medullary carcinoma area showed calcitonin. Besides, this type of tumor should be differentiated from some rare thyroid tumors, such as MTC papillary subtype, island follicular carcinoma, neuroendocrine carcinoma, paraganglioma, etc. Immunohistochemical markers can provide in the identification of the above tumors.

The current diagnostic and treatment standards for thyroid cancer do not supply precise and individualized treatment plans for medullary cancer combined with papillary cancer. The main focus is on surgical operations. Postoperative papillary cancer can be supplemented with radioactive iodine and endocrine treatment. Medullary cancer is radiotherapy, chemotherapy, and endocrine therapy that are not sensitive, and standardized surgical procedures are currently the most effective means [8]. This patient had medullary carcinoma on one side and papillary microcarcinoma on one side. She underwent bilateral total thyroidectomy plus bilateral central area lymph node dissection. Serum calcitonin and CEA were regularly monitored after the operation. An increase in the two implied a poor prognosis or tumor recurrence.

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### **Conflicts of Interest**

The authors declare no conflicts of interest regarding the publication of this paper.

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