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Case Report

Two Cases of Mixed Medullary and Follicular Cell Carcinoma with Literature Review

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Abstract: Mixed Medullary and Follicular Cell Carcinoma (MMFCC) is a rare thyroid cancer combining medullary and follicular (often papillary) elements. The lack of standard clinical signs and imaging characteristics makes it difficult to diagnose before surgery. At present, the main approach to treatment is surgical removal, and the outlook for patients is primarily influenced by how advanced the medullary carcinoma is. We report two cases of MMFCC confirmed by postoperative pathology. Case 1 involved a 46-year-old woman with bilateral thyroid nodules and left cervical lymph node metastasis. Preoperative ultrasound classified the nodules as TI-RADS 4c, and fine-needle aspiration cytology suggested papillary thyroid carcinoma. Total thyroidectomy with bilateral neck lymph node dissection was performed. Postoperative pathology revealed MMFCC, with a medullary component accounting for approximately 95% and extensive lymph node metastasis. Six weeks postoperatively, serum calcitonin was 73.00 pg/mL. Case 2 involved a 54-year-old man presenting with neck pain. Ultrasound showed a hypoechoic left thyroid nodule (TI-RADS 4b) with bilateral cervical lymphadenopathy. Fine-needle aspiration suggested medullary thyroid carcinoma, and serum calcitonin and carcinoembryonic antigen levels were markedly elevated. Following total thyroidectomy with bilateral neck lymph node dissection, pathology confirmed MMFCC with an approximately 80% medullary component. Postoperative tumor markers decreased significantly, and long-term follow-up was initiated. MMFCC is a rare thyroid carcinoma with considerable diagnostic difficulty. Fine-needle aspiration alone may be insufficient for accurate diagnosis, whereas preoperative serum calcitonin testing provides important diagnostic clues. Total thyroidectomy with systematic lymph node dissection is advised, plus long-term monitoring per both carcinoma guidelines.

Keywords: Mixed Medullary and Follicular Cell Carcinoma; Thyroid; Mixed Tumor

1. Introduction

In recent decades, the global incidence of thyroid cancer has seen a significant surge, particularly in differentiated types. However, death rates have not changed much, which can be linked to improvements in detection and treatment methods. As the most prevalent endocrine malignancy and a key head-and-neck tumor, thyroid cancer shows great diversity across histological subtypes. This affects its cause, behavior, therapies, and outcomes [1].

PTC is the most common type of thyroid cancer, making up roughly 85% to 90% of all cases. It develops from the follicular epithelial cells of the thyroid. In contrast, MTC, originating from parafollicular cells, is far less common, comprising just 2%–4% of cases [2–4]. These two malignancies of distinct origins—PTC and MTC—can indepen-

dently coexist within the same patient, presenting as either collision tumors or mixed as a tumor showing dual differentiation. According to the WHO classification, the latter is termed MMFCC, a rare pathological condition [5].

MMFCC does not present with standard clinical signs or imaging characteristics, which complicates its diagnosis before surgery. Fine-needle aspiration cytology often falls short in accurately identifying this mixed tumor, while preoperative serum calcitonin testing is crucial for detecting the MTC component. At present, the main approach to treating MMFCC is surgical removal, yet there are no established guidelines regarding the ideal extent of surgery or postoperative care. The outlook for patients is largely influenced by the MTC component and its stage.

This paper presents two cases of MMFCC. By analyzing their clinical and pathological data, diagnostic and therapeutic processes, and follow-up outcomes, as well as reviewing relevant literature, we aim to explore the clinical characteristics, diagnostic approaches, treatment strategies, and prognosis of MMFCC. This study seeks to enhance clinicians' understanding and management of this rare disease (**Figure 1**).

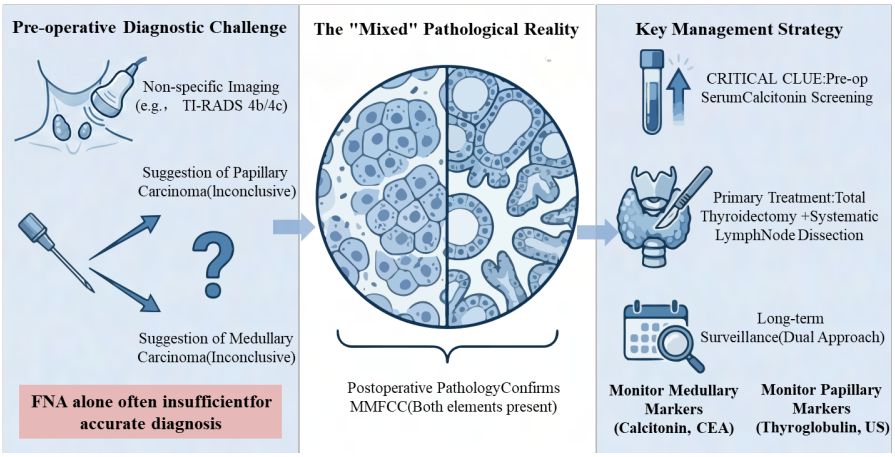

Figure 1. Diagnostic Challenges and Management Strategy for MMFCC.

Figure 1 summarizes the clinical pathway for MMFCC based on the reported cases. Left Panel: Illustrates the pre-operative diagnostic dilemma where standard ultrasound (TI-RADS categorization) and FNA often fail to identify the mixed nature of the tumor, leading to inconclusive results. Middle Panel: Depicts the defining pathological characteristic of MMFCC—the coexistence of distinct medullary (calcitonin-positive) and follicular/papillary (thyroglobulin-positive) cell populations. Right Panel: Highlights the key management strategies, emphasizing the critical role of pre-operative serum calcitonin screening, the necessity of total thyroidectomy with systematic lymph node dissection, and a dual-surveillance approach monitoring markers for both carcinoma types postoperatively.

2. Pathological Evaluation and Diagnostic Consensus

For both cases, the diagnosis of MMFCC was established through a consensus process. Histopathological slides and immunohistochemical staining results were independently reviewed by at least two senior pathologists with extensive experience in thyroid tumors. In cases of disagreement, a pathology consultation meeting was convened to reach a final consensus. The diagnosis was based on the distinct morphological characteristics of the medullary and follicular components, as well as their respective immunoprofiles: Calcitonin, CD56, and Synaptophysin positivity for the medullary component, and CK19, Galectin-3, and HBME-1 positivity for the follicular (papillary) component. This procedure ensured the accuracy and reliability of the MMFCC diagnoses reported in this study.

3. Case Presentation

3.1. Case 1

A 46-year-old woman was admitted for evaluation of a thyroid mass that had been detected two years earlier. She did not exhibit symptoms such as hoarseness, difficulty swallowing, palpitations, fever, or weight loss. Physical examination revealed a non-tender, mobile nodule measuring approximately 2.0 × 1.5 cm in the left thyroid lobe.

Enlarged lymph nodes were also detected on the left side of the neck. A thyroid ultrasound showed a hypoechoic nodule measuring around 2.5 × 1.7 × 1.4 cm in the midsection of the left lobe, along with another hypoechoic nodule of 0.39 × 0.38 cm in the mid-right lobe. Both nodules had irregular shapes and poorly defined edges, with a longitudinal-to-transverse ratio exceeding 1. Additional hypoechoic and mixed-echo nodules were noted throughout the thyroid, the largest being 1.0 × 0.5 cm, all with well-defined borders. Multiple enlarged lymph nodes were found in the left neck regions II–IV and VI, the largest measuring 1.0 × 0.7 cm, all showing indistinct capsules. Diagnostic imaging indicated bilateral mid-thyroid lobe hypoechoic nodules (TI-RADS 4c), other thyroid nodules (TI-RADS 3), and enlarged lymph nodes in the left neck that were suspected to be malignant. Fine-needle aspiration cytology confirmed the presence of malignant cells in the left cervical lymph node and a malignant tumor (Bethesda Class VI) in both the left and right thyroid lobes, diagnosed as PTC. After excluding surgical risks, the patient underwent a total thyroidectomy along with bilateral level VI and left levels II–V lymph node dissection. During surgery, an enlarged lymph node was observed on the recurrent laryngeal nerve, which was firm and adhered to the nerve, and was subsequently dissected. The nerve monitoring indicated that nerve function was preserved. Both the bilateral parathyroid glands and recurrent laryngeal nerves were carefully dissected and preserved. The thyroid gland and tumor were entirely removed, with no residual tumor detected, and the parathyroid glands remained intact. Postoperative pathology revealed a mixed medullary-follicular carcinoma, composed of approximately 95% medullary component and 5% follicular cell-derived component with PTC morphology in the left thyroid lobe and classic PTC in the right lobe. Metastatic lesions were found in the left zones 3, 4, 5, and 6 lymph nodes, while no metastases were detected in the right zone 6 and left zone 2 lymph nodes. Immunohistochemical analysis showed CK19 (focal+), Galectin-3 (focal+), Calcitonin (mostly+), CD56 (mostly+), TTF-1 (+), Pax-8 (focal+), HBME-1 (+), TG (−), and Syn (mostly+) (**Figure 2**). In Case 1, although the medullary component accounted for approximately 95% of the tumor, the minor papillary component (approximately 5%) was confirmed as true PTC based on classic nuclear features (enlargement, overlapping, chromatin clearing, nuclear grooves) and a supportive immunoprofile (CK19+/Galectin-3+/HBME-1+, TG−, Calcitonin−). This component was clearly distinct from the medullary component (Calcitonin+/CD56+/Syn+, mostly+). Morphological and immunohistochemical segregation, together with preoperative FNA and the presence of contralateral PTC, support a genuine papillary component rather than entrapped thyroid follicles. The patient has been regularly followed up postoperatively and has not experienced any symptoms of hoarseness, difficulty swallowing, or hand-foot convulsions.

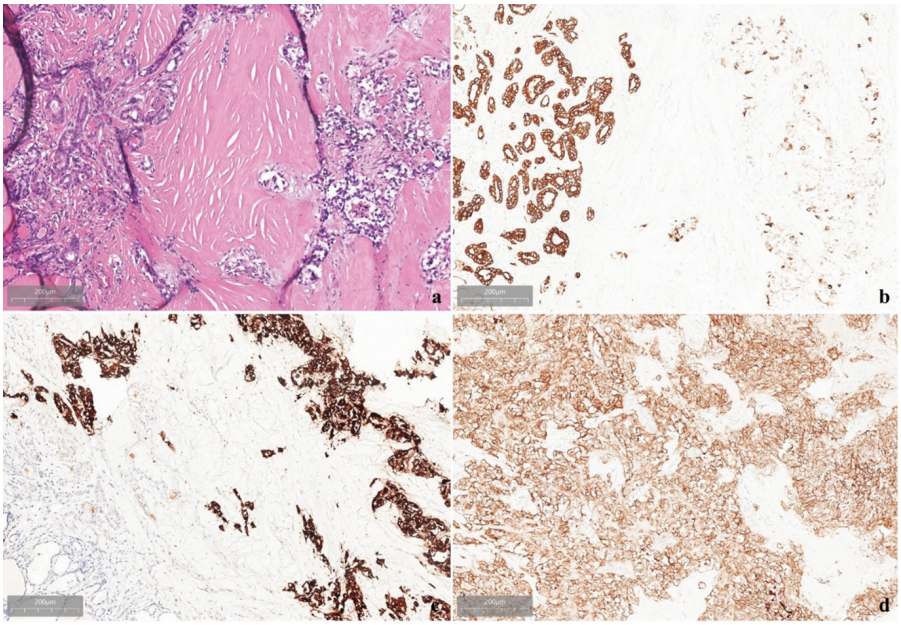

Figure 2. HE and immunohistochemical staining in Case 1. (**a**) HE staining of PTC and MTC (200×); (**b**) CK19 staining shows strong positivity in PTC and weak positivity in areas of MTC (200×); (**c**) Syn staining shows negative for PTC and positive for MTC (200×); (**d**) CD56 staining demonstrates positivity for MTC (200×).

3.2. Case 2

A 54-year-old man was hospitalized due to experiencing neck pain and discomfort for the past ten days. Upon examination, he exhibited tenderness but did not show signs of hoarseness, difficulty swallowing, palpitations, fever, or weight loss. The initial assessment revealed a Grade I enlargement of the thyroid. A firm, ill-defined mass measuring around 2 cm was detected in the middle of the left lobe, which moved during swallowing and was non-tender. Additionally, several enlarged lymph nodes were found in the left supraclavicular area, with the largest measuring approximately 2 × 1 cm, characterized as firm and relatively well-defined. A thyroid ultrasound indicated a 2.7 × 1.7 cm hypoechoic lesion in the mid-left thyroid lobe, irregularly shaped with indistinct edges and containing scattered hyperechoic foci. Bilateral hypoechoic masses were also identified in the neck, with the largest located in region IV: left (2.6 × 1.2 cm) and right (1.8 × 0.9 cm), both having irregular shapes and clear margins. Most structures appeared poorly defined, with minimal linear medullary components visible. The diagnosis suggested heterogeneous thyroid changes indicative of Hashimoto's thyroiditis, a hypoechoic area in the mid-left thyroid lobe (TI-RADS 4b), and bilateral cervical hypoechoic masses, along with "M" lymph nodes. A fine-needle aspiration biopsy of the left thyroid lobe hypoechoic area and lymph nodes from both sides revealed moderately proliferating follicular epithelial cells with atypical features, including a partially spindle-shaped arrangement and visible nucleoli, indicating medullary carcinoma. After ruling out surgical contraindications, the patient underwent a total thyroidectomy along with bilateral lymph node dissection in regions VI and II–V. The right recurrent laryngeal nerve was preserved and monitored during surgery, showing good function, while the left recurrent laryngeal nerve was infiltrated by the tumor, necessitating the resection of about 2.0 cm of the affected segment. Both superior and inferior parathyroid glands were retained. Postoperative pathology revealed a mixed medullary-follicular cell carcinoma in the left thyroid lobe, consisting of approximately 80% medullary component and 20% follicular cell-derived component with papillary thyroid carcinoma morphology, and a similar finding in the right lobe. Metastatic carcinoma was identified in regional lymph nodes from zones 2–7 on the left and zones 2–6 on the right. Immunohistochemical analysis of the papillary carcinoma component showed CK19 positivity, while Calcitonin, CD56, CgA, and Syn were negative; the medullary carcinoma component was weakly positive for CK19, and positive for Calcitonin, CD56, CgA, and Syn, with BRAF V600E being negative. Special staining with Congo red was positive. After surgery, the patient reported no hoarseness, difficulty swallowing, or discomfort such as hand-foot convulsions.

In Case 1, preoperative serum calcitonin was not measured because medullary thyroid carcinoma was not suspected prior to surgery. Six weeks postoperatively, serum calcitonin was 73.00 pg/mL, exceeding the reference range (0–18 pg/mL). During the two-month follow-up after surgery, there were no signs of tumor recurrence or metastasis. In Case 2, the preoperative serum calcitonin was recorded at 4471.99 pg/ml, with a CEA level of 598.20 ng/ml. By postoperative day 2, serum calcitonin had decreased substantially to 1204.12 pg/mL, accompanied by a reduction in CEA to 443.60 ng/mL. A five-year follow-up, which included several thyroid ultrasounds, CT scans, and blood tests, showed no indications of metastasis. Both patients received oral levothyroxine therapy for hormone replacement after their surgeries.

4. Discussion and Conclusion

Thyroid cancers are the most prevalent tumors within the endocrine system. Approximately 95% of these malignancies are differentiated thyroid carcinomas (DTC), originating from follicular cells, encompassing papillary and follicular carcinomas [2–4]. PTC stands out as the most prevalent, accounting for roughly 85% of DTC cases [1]. This type of cancer typically grows slowly and can remain confined to its original location for many years, often first spreading to nearby cervical lymph nodes. Small PTC foci are frequently discovered during autopsies, with estimates suggesting their presence in up to 30% of adults [3]. In stark contrast, MTC is far less common, arising from neuroendocrine C cells (parafollicular cells) and representing about 2% to 4% of thyroid cancers [6,7]. In 1988, the World Health Organization defined MMFCC as a tumor displaying both medullary and follicular carcinoma features, with immunoreactivity for calcitonin and thyroglobulin, respectively. The follicular cell-derived component can include papillary, follicular, oncocytic, poorly differentiated, or anaplastic carcinoma. The etiology of MMFCC remains elusive, with several theories proposed, a common stem cell differentiating into two tumors (stem cell theory), medullary carcinoma differentiating into follicular epithelium (divergent differentiation theory), simultaneous carcinogenic stimuli affect-

ing follicular epithelium and C cells in a specific area (field effect theory), collision between separately developed follicular epithelial tumors and medullary carcinoma (collision effect theory), and incorporation of normal follicular cells into medullary carcinoma leading to tumorigenesis (hostage theory) [8]. The case presented in this article aligns with one of these theories.

Patients with MMFCC containing a papillary thyroid carcinoma component are difficult to diagnose solely based on clinical manifestations. Studies indicate that on ultrasound, they mostly appear as hypoechoic or very hypoechoic nodules with microcalcifications [9]. FNA typically diagnoses PTC or suspected carcinoma. However, for patients with both MTC and PTC, FNA cytology's diagnostic value is limited, as detecting both types simultaneously is difficult [10–14]. In this report, preoperative FNA misdiagnosed PTC and MTC, aligning with prior studies [15–18].

Surgical treatment stands as the most effective strategy for thyroid cancer, though the concurrent occurrence of MTC and PTC is uncommon [19]. Globally, specialists have yet to reach a consensus on the optimal surgical extent, with current guidelines lacking specific advice for this scenario [9]. The coexistence of medullary and follicular cell-derived components within MMFCC does not change the epidemiological or pathological characteristics, nor the unique clinical features of these cancer types; rather, the prognosis is mainly influenced by the stage of MTC at the time of diagnosis [20]. Given MTC's unfavorable prognosis, surgery is crucial for disease management [5,20,21]. Current protocols emphasize preoperative calcitonin testing for patients with newly discovered thyroid nodules [22]. Early serum calcitonin assessment during nodule evaluation can swiftly identify MTC, aiding in more suitable surgical planning and potentially reducing postoperative morbidity [23]. Both the ATA and NCCN guidelines advocate total thyroidectomy with central neck dissection as the standard for MTC, while lobectomy indications remain unclear [24,25]. In our observations, Case 1 revealed bilateral PTC confirmed through preoperative FNA, while Case 2 indicated potential bilateral cervical lymph node metastasis via preoperative FNA. Both patients underwent total thyroidectomy to facilitate central neck lymph node dissection. Considering MMFCC's dual tumor nature, postoperative care may include radioactive iodine therapy, endocrine treatments, and targeted drug therapies [26]. Some research suggests radiotherapy and chemotherapy could induce local remission in advanced cases, though larger studies are needed for validation [27]. Additionally, patients with mixed-type carcinoma may have better survival rates than those with pure medullary carcinoma [2,9].

At present, there are no standardized management protocols for mixed cell thyroid tumors. Therefore, patients with this rare disease should be monitored in accordance with the established monitoring principles applicable to each tumor component. Necessary evaluations include the measurement of serum procalcitonin, carcinoembryonic antigen, and thyroglobulin levels, as well as thyroid function tests and neck ultrasound examinations. If necessary, additional imaging such as CT or PET scans should be used to detect recurrence or metastasis [26].

In conclusion, MMFCC is a rare thyroid tumor with indistinct clinical features and minimal differences in ultrasonography and other tests. The prognosis is mainly linked to the clinical stage of MTC and the stage at which it is diagnosed. Consequently, surgical removal is the most recommended approach for patients with MMFCC. The role of postoperative adjuvant therapies, including chemoradiation, radioactive iodine, endocrine therapy, and targeted agents, warrants further investigation.

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Institutional Review Board Statement

Because the study was conducted as retrospective case series, it did not require ethical approval.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The authors confirm that the data associated with the experiments can be made available upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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