CLINICAL COMMENTARY

Mixed Medullary Follicular Thyroid Carcinoma: Case Presentation and Review of Literature

Na Shen, M.D., and Dorothy Martinez, M.D.

Abstract

Mixed medullary follicular carcinomas (MMFC) of the thyroid are rare tumors. Surgery has been the accepted first line of treatment; however, adjunctive treatment with radioactive iodine has been considered, though it is controversial due to the limited number of cases. There are few cases reported of MMFC patients treated initially with surgery followed by radioactive iodine ablation without subsequent signs of recurrence or metastasis. We report a patient with MMFC with lymph node metastasis successfully treated with radioactive iodine ablation after surgery. The patient is currently disease free 4 years after initial diagnosis. This demonstrates a potential role for I-131 as adjunctive therapy following surgery in patients with lymph node thyroglobulin positive disease.

Introduction

Medullary thyroid carcinomas (MTC) are derived from the parafollicular (C cells) of the thyroid and composed of a population of cells with neuroendocrine differentiation. They comprise only about 5-10% of all thyroid carcinomas and secrete calcitonin while expressing CEA.[1] Follicular and papillary thyroid carcinomas are derived from follicular cells of the endoderm and account for over 90% of all thyroid cancers.[1] Extremely rare tumors that exhibit the morphological and immunohistochemical features of both medullary thyroid carcinoma and follicular carcinoma have been termed "mixed medullary follicular carcinoma (MMFC)".[2] These tumors not only pose diagnostic challenges given their various presentations, but treatment is also debatable. Surgery has been the accepted first line of treatment; however, there has been no consensus on adjunctive treatment with I-131. We report a case of MMFC with lymph node metastasis that was successfully treated with surgery followed by radioactive iodine ablation.

Case Report

The patient is a 55-year-old female who presented with a left thyroid nodule 4 years ago. She underwent fine needle aspiration (FNA) biopsy of this nodule at an outside institution, which reported a Hurthle cell lesion. A subsequent left thyroid lobectomy was performed, which showed a 1.6 cm thyroid nodule with features concerning for mixed medullary

follicular carcinoma (MMFC). She came to UCLA for further evaluation. Review of the FNA was interpreted as a follicular neoplasm with cytologic features suggestive of medullary thyroid carcinoma (MTC). The lobectomy specimen revealed a neoplasm consisting principally of MTC with scant intimately admixed follicular-derived cell clusters, favoring a diagnosis of MMFC. The MTC component exhibited positive immunohistochemical staining for calcitonin, chromogranin, synaptophysin, TTF-1, and carcinoembryonic antigen (CEA). In addition, rare foci of MTC showed thyroglobulin positivity. The follicular-derived cell clusters expressed thyroglobulin and TTF-1. No extrathyroidal extension nor lymphovascular invasion was identified. Margins were free of tumor. The patient was also evaluated for hypercalcemia and pheochromocytoma with negative work up. She had a completion thyroidectomy, central neck dissection, and left modified radical neck dissection. The right thyroid gland was negative for carcinoma. However, 4 of 24 total lymph nodes, including neck lymph nodes at left level 4 and right level 6, obtained showed metastatic MMFC. Similar to the primary thyroid tumor, the metastatic carcinoma was composed largely of the MTC component (>90% of the neoplasm) with scant foci of follicular cells. The metastatic carcinoma in the lymph nodes showed diffuse immunopositivity for TTF-1, CEA, synaptophysin, chromogranin, and calcitonin. Additionally, strong thyroglobulin staining was observed in rare colloid-producing follicular cells and a rare focus of MTC.

The patient's thyroglobulin level at the time was 0.4ng/mL (normal 3-40ng/ml) with thyroid antibody of <1 IU/mL (normal <2.5 IU/mL) and TSH of 3.4mcIU/mL (normal 0.3-4.7 mcIU/mL). The initial calcitonin level prior to the first surgery was not available for review but was reported to be normal.

The patient received 154.4mCi of I-131. Whole body scan after radioactive iodine treatment showed large tracer activity within the thyroid bed as well as focus of iodine avid disease substernally consistent with level 6 metastasis. Subsequent serial thyroglobulin levels have remained undetectable at <0.2ng/mL, and calcitonin levels have also remained undetectable at <2pg/mL (normal <5.1). Carcinoembryonic antigen (CEA) remained normal at 3.1ng/mL (normal <3.1ng/ml). Serial neck ultrasounds since have also remained

negative for masses or abnormal lymph nodes. The patient remains on suppressive levothyroxine therapy with TSH targeted between 0.1-0.5 mcIU/ml. She tested negative for the RET mutation. She is now more than four years since her thyroidectomy and radioactive iodine therapy, and she still remains free of signs of cancer recurrence or metastasis.

Discussion

In the late 1970s, some medullary thyroid carcinomas were noted to have "atypical" histological appearance with follicular structures in addition to the typical medullary features. In addition to the characteristic calcitonin immunoreactivity in these MTCs, thyroglobulin was also detectable in the foci that had a follicular appearance.[3] A new entity was then proposed termed "mixed medullary follicular carcinoma" (MMFC). The classic WHO definition for this tumor is "a tumor showing both the morphological features of medullary carcinoma together with immunoreactive calcitonin and the morphological features of follicular carcinoma together with immunoreactive thyroglobulin."[4]

MMFCs are extremely rare tumors representing less than 0.15% of all thyroid tumors. The reported median patient age is 48 years. The majority of these tumors occur in sporadic form, and the remainders appear as a component of hereditary syndromes such as MEN2. MMFC may affect either thyroid lobe or the isthmus and are usually unifocal. Multifocal tumors have only been observed in cases of MEN2A patients.[5] Most MMFC cases have lymph node involvement, and in cases with disease progression, distant metastases have been reported in the lung, liver, mediastinum, and bone.[6]

Embryologically, MTCs and follicular carcinomas have distinct origins, which make the histogenesis of MMFCs extremely fascinating. Thyroid follicular cells are most likely derived only from the median of the thyroid anlage, which is an enclosed group of endodermal cells located on the midline of the embryologic mouth cavity.[7] Meanwhile, C cells originate in the ultimobranchial body, which corresponds to the fourth and fifth pharyngeal pouch.[8] The favored theory for the histogenesis of MMFC is the stem cell hypothesis, which describes an uncommitted stem cell as capable of differentiating towards both follicular and C cell lineage.[9] The ultimobranchial body has been proposed as the source of common stem cell as nests of these cells in the thyroid have been shown to be immunoreactive to both thyroglobulin and calcitonin in animal studies.[2,10] Studies of chicken and dog thyroid have shown ultimobranchial remnants giving rise to both thyroid follicles and C cells.[11] To further support this theory, a few case reports have shown individual tumors co-expressing calcitonin and thyroglobulin at both the protein and mRNA levels.[6,9]

Other hypotheses have also been proposed to explain the mixed patterns of MMFC.[9] According to the divergent differentiation hypothesis, some MTC cells differentiate towards a follicular phenotype by the acquisition of additional molecular defects. The field effect hypothesis describes a common oncogenic stimulus triggering neoplastic transformation of both follicular and C cells. In the collision theory, it is hypothesized that two independently arising tumors collide in the thyroid. However, direct evidence supporting these hypotheses is limited. A newer hypothesis termed the hostage theory has been proposed by Volante et al[9] based on their molecular analyses of the two histological components in 12 MMFC cases. They proposed that entrapped non-neoplastic follicles are stimulated by trophic factors leading to a hyperplastic follicular focus. These follicular cells then acquire genetic defects leading to neoplastic transformation and development of follicular or papillary carcinoma components that can give rise to mixed metastasis.[9]

RET proto-oncogene mutations may also play a role in the pathogenesis of MMFC. RET proto-oncogene mutations that are similar or different from those detected in sporadic and familial medullary thyroid carcinoma have also been found in a limited number of MMFC cases. Volante et al[9] analyzed RET mutations in 11 MMFC patients and found two known MEN2A cases with an expected mutation at exon 10 codon 618. In that series, two cases also had somatic mutations at exon 16 codon 918 similar to those found in sporadic MTC.[9] One case of MMFC has also been described where RET analysis revealed a new variant in exon 13 R770Q.[12]

Unfortunately, the biologic behavior of MMFC is difficult to predict. Papotti et al[6] reviewed 15 MMFC cases and found that 53.3% of the patients had aggressive disease and had either died or were alive with tumor progression at follow-up. In the same review, 40% of the patients had no evidence of disease at 1-2 year follow-up. In Papotti et al's[13] largest reported MMFC series of 11 patients, they found that 5 out of 10 patients had died of their tumor or were alive with active disease at follow-up. In 4 of the same 5 cases, elevated serum calcitonin levels were documented at time of relapse indicating the tumor was probably behaving as a MTC.[13] In another interesting case, an MMFC patient developed extensive metastatic deposits, which produced thyroid hormones causing thyrotoxicosis.[14]

Treatment in MMFC is debatable given the limited number of cases and unclear biologic behavior of these tumors. Surgery is accepted as the first line treatment; however, there is no agreement on adjuvant therapy including radioactive iodine and chemotherapy. Theoretically, the presence of positive thyroglobulin immunohistochemical staining in MMFC indicates a role for I-131. In the case series by Papotti et al,[13] only one single case was treated with radioactive iodine at the time of recurrence but with poor iodine uptake. In the MMFC case report with metastatic deposits producing thyroid hormones, the patient had received I-131 following surgery

with initial response but eventually died due to extensive metastatic disease.[14] One of the earliest MMFC cases reported the patient receiving surgery followed by I-131 but developed recurrence only 2 years later.[15] A more recent case indicated a good response with I-131 after surgery; however, their follow-up was only 1 year after initial diagnosis, so longer outcomes of the ablative radiation therapy are unclear.[11]

In conclusion, we report a case of mixed medullary follicular carcinoma with positive immunohistochemistry for calcitonin and thyroglobulin in both the primary tumor and metastasis. The patient received surgery followed by radioactive iodine ablation with no signs of recurrence 4 years from initial diagnosis. To our knowledge, this is the longest duration of disease-free survival in an MMFC patient treated initially with both surgery and I-131. The clinical outcome of this case provides more evidence for the use of adjuvant radioactive iodine in these extremely rare tumors.

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