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Synchronous multifocal medullary and papillary thyroid microcarcinoma detected by elastography☆

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ABSTRACT

INTRODUCTION: A few cases of concomitant medullary and papillary carcinoma in the same thyroid nodule have been described in the literature. However, the presence of multiple foci of both types of malignancy in the same gland is very rare.
PRESENTATION OF CASE: A 39 year-old female with multiple thyroid nodules, elevated serum calcitonin levels and elastographic findings suggestive of thyroid malignancy, underwent total thyroidectomy and central neck dissection. Histology revealed the presence of one focus of medullary and one focus of papillary carcinoma on each thyroid lobe. Subsequently, the patient underwent treatment with radioactive iodine.
DISCUSSION: This is the third case of synchronous multifocal medullary and papillary thyroid carcinoma reported in the literature. Several theories for the simultaneous development of these malignant entities have been proposed.
CONCLUSION: Ultrasound elastography can be a useful, noninvasive tool in the assessment of thyroid nodules.

1. Introduction

Thyroid cancer accounts for 1–2% of all malignancies, representing the most common endocrine malignancy.[1] Papillary carcinoma (PTC) is the most frequent among thyroid malignancies, whereas medullary thyroid carcinoma (MTC) accounts for 5–10% of cases.[2] These two histological types have different embryological origin. PTC derives from the follicular cells of the endoderm.[3] MTC, on the other hand, originates from parafollicular cells of the ultimobranchial body, derived from the fourth pharyngeal pouch.[4] MTC is divided in hereditary and sporadic forms. Hereditary MTC can manifest either alone as familial MTC or as part of the multiple endocrine neoplasia type 2 syndromes (MEN 2).[4] MEN 2 involves medullary carcinoma and pheochromocytoma with either primary hyperparathyroidism (MEN 2A) or marfanoid habitus and mucosal neurofibromatosis (MEN 2B). Concurrence of medullary and papillary thyroid carcinomas is an unusual finding. In this report, a case of multifocal thyroid cancer involving two foci of medullary and two foci of papillary microcarcinomas is presented.

2. Presentation of case

A 39 year-old female presented for otorhinolaryngologic evaluation at the outpatient clinic of a tertiary referral center (Department of Otorhinolaryngology, University Hospital of Heraklion, Greece). Patient was referred by a general practitioner following an abnormal neck ultrasound study. The examination had been performed as part of a routine assessment for reported difficulty in swallowing and neck discomfort complaints by the patient. It had revealed slightly enlarged thyroid gland lobes, with presence of two nodules in the right lobe of the gland (maximum diameter 0.3 cm and 0.8 cm, respectively) and two nodules in the left lobe (maximum diameter 0.4 cm and 0.6 cm, respectively). All nodules demonstrated increased peripheral vascularization and irregular boundaries, without any spot microcalcifications. Ultrasound elastography had been used to complete the imaging study and revealed suspicious findings, with an elastography score of 4 in one, and 5 in all other nodules. Previous medical history was free. Patient denied any past exposure to radiation as well as any family history of endocrine disorders. Clinical examination of the head and neck was unremarkable, and no masses were noted on palpation of the neck. Serum levels of calcium, thyroid stimulating hormone (TSH), free thyroxine and thyroglobulin as well as

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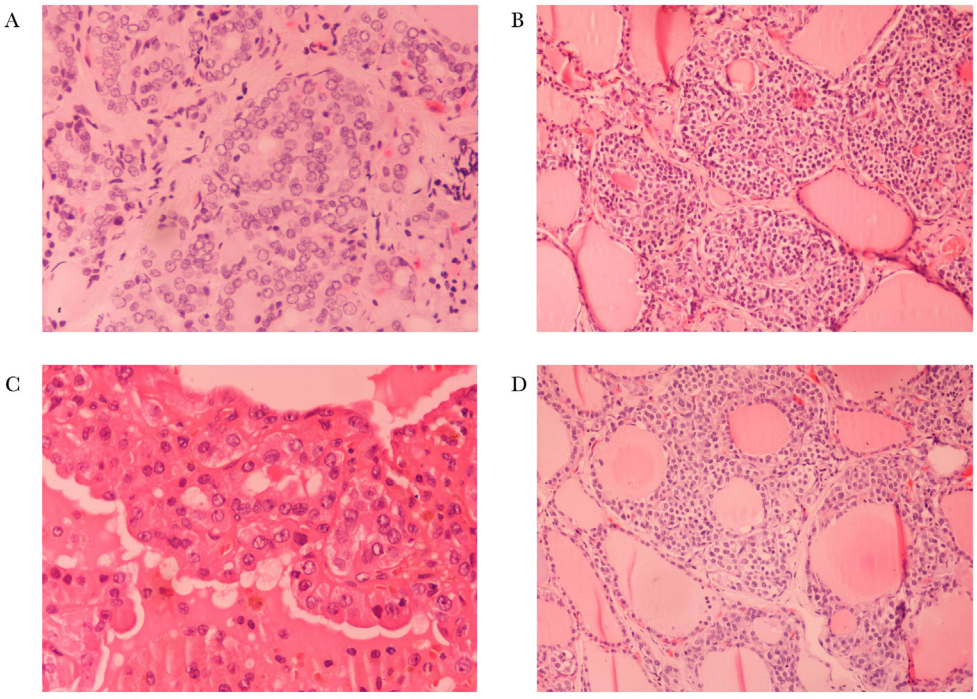

Fig. 1. Microscopic view of multiple foci of thyroid carcinoma. (A) Papillary microcarcinoma of the right lobe (Hematoxylin–eosin stain, original magnification ×400). (B) Medullary carcinoma of the right lobe (Hematoxylin–eosin stain, original magnification ×200). (C) Papillary carcinoma of the left lobe (Hematoxylin–eosin stain, original magnification ×400). (D) Medullary carcinoma of the left lobe (Hematoxylin–eosin stain, original magnification ×200).

parathyroid hormone were within normal range. Calcitonin levels, on the other hand, were increased (86 pg/ml; normal values: <12 pg/ml in women). Abdominal ultrasound did not show any adrenal pathology and urinary catecholamines and metanephrine levels were within normal limits. Ultrasound guided fine-needle aspiration (FNA) cytology of the thyroid was performed twice, but was non-diagnostic. After discussion with the patient, performance of total thyroidectomy was decided. This decision was based on increased levels of calcitonin in addition to findings on elastography that were suggestive of thyroid malignancy. Patient underwent surgery under general anesthesia. A transverse cervical incision was performed, subplatysmal flaps were raised and strap muscles were separated in the midline. Both lobes were completely removed after recognition and meticulous dissection of the recurrent laryngeal nerves. Four parathyroid glands were recognized and preserved. A prophylactic bilateral central neck dissection was also performed bilaterally. Postoperative course was uneventful and the patient was discharged from the hospital two days after surgery.

Permanent histology of the specimen described the presence of two microscopic foci of medullary carcinoma as well as two papillary microcarcinomas. More specifically, a papillary microcarcinoma (diameter: 7 mm) (Fig. 1A) and a microscopic medullary carcinoma (diameter: 1.3 mm) (Fig. 1B) were found in the right lobe, while hyperplastic C cells were detected next to the tumors. In the left lobe, a 4 mm papillary carcinoma was found (Fig. 1C), as well as a microscopic medullary carcinoma with a diameter of 3.5 mm (Fig. 1D). No invasion of the thyroid capsule was noted. Lesions of nonspecific lymphocytic thyroiditis were demonstrated bilaterally. Eleven lymph nodes had been removed, and all were found free of metastasis on histopathological examination. Tumor tissue examination for the RET oncogene mutations was negative. Due to multifocality of the papillary carcinoma, the patient underwent treatment with 100 mCi of radioactive iodine (^{131}I) six weeks after surgery. Ten months later, the patient is under TSH suppression treatment with levothyroxine and retains low levels of thyroglobulin and calcitonin. No signs of recurrent disease are noted ten months after surgery.

3. Discussion

Thyroid cancer is the most common endocrine malignancy, accounting for more than 90% of malignancies of the endocrine glands.[1] Well-differentiated thyroid cancer, including papillary and follicular carcinomas, remains the most common thyroid malignancy, whereas medullary and anaplastic carcinomas represent 5–10% and 1.6% of cases, respectively.[2]

Various genetic disorders have been implicated in thyroid tumorigenesis. Mutations of the RET oncogene are involved in almost all forms of hereditary MTC.[5] The most common mutations described in well-differentiated thyroid carcinomas involve the BRAF gene, and are observed in 36–69% of cases.[6] Multifocality of both medullary and papillary components is a rare entity, and only two cases have been previously described in the literature.[7] The concurrence of PTC and MTC is an interesting phenomenon as these tumors have different embryological origin. MTC originates from C cells of the ultimobranchial body, derived from the fourth pharyngeal pouch, whereas PTC originates from follicular epithelial cells, derived from median endodermal analogs. Several theories for this coexistence have been proposed. According to the "stem cell theory," uncommitted stem cells differentiate into both follicular and C-cell lineages.[8] The "divergent differentiation theory" states that C cells and thyroid follicles are derived from remnants of the ultimobranchial body and solid cell nests.[9] The "field effect theory" suggests that simultaneous transformation of both follicular and C cells is a result of common neoplastic stimuli.[10] Finally, the "collision theory" suggests that two independent tumors are located in the same lesion by simple coincidence.[11]

Cytological examination of material obtained by FNA represents the best single diagnostic test for differentiating malignant from benign thyroid lesions. FNA is characterized by high sensitivity and specificity.[12] However, the necessity for a reliable noninvasive

diagnostic procedure still remains. Elastography is a newly developed imaging technique that uses ultrasound to estimate tissue stiffness by measuring the degree of distortion under the application of an external force.[13] It is based upon the principle that softer components of tissues deform easier than harder components under compression, thus allowing an objective determination of tissue consistency. Elasticity of thyroid nodules is evaluated according to the Rago classification system using a scale of 1–5. Score 1 indicates high elasticity in the whole nodule; score 2 indicates elasticity in a large part of the nodule; in score 3 elasticity is detected only at the peripheral part of the nodule; no elasticity in the nodule is detected in score 4; score 5 indicates no elasticity in the nodule as well as the posterior shadowing.[13] Scores 1–3 are generally associated with benign lesions, while scores 4–5 are suggestive of malignancy. Ultrasound elastography demonstrates high sensitivity (97%) and specificity (100%) in the diagnosis of thyroid malignancy, with the predictive value of the examination being independent from the nodule size. Thus, elastography can be a reliable, noninvasive tool in the differential diagnosis of thyroid nodules. In the case presented here, the decision to perform an FNA and furthermore a thyroidectomy was largely based on the suspicious findings of elastography.

Surgery remains the mainstay of treatment for thyroid cancer. Total or near total thyroidectomy is the preferred procedure for both PTC and MTC, since thyroid lobectomy is associated with a higher risk of recurrence.[14,15] Therapeutic central neck dissection should be performed in cases of pathologic lymph node involvement noted on preoperative clinical and imaging assessment.[12] On the other hand, prophylactic central neck dissection is still a matter of debate. Multifocality of PTC constitutes a risk factor for lymph node metastasis.[16] Thus, a prophylactic central neck dissection should be considered in patients with multifocal PTC, as in the case of our patient.

4. Conclusion

Development of multiple, small foci of different histological types of thyroid carcinoma is a rare event. Elastography can be a useful and noninvasive tool in the differential diagnosis of small thyroid nodules.

Conflict of interest

No competing interests declared.

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None.

Ethical approval

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

George Velegrakis and Alexander Karatzanis performed the surgery. Eleftherios Koudounarakis wrote the manuscript. Alkiviadis Chatzidakis reviewed the literature. Maria Tzardi provided the histological images.

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