CASE REPORT

Synchronous papillary thyroid carcinoma and medullary thyroid carcinoma – a pitfall waiting to happen

TANG Po Yin FRCPath, FRCPA, KHOR Li Yan MBCh, ABP AP/CP and Cytopathology and Angela TAKANO MD, ABP AP/CP and Cytopathology

Department of Anatomical Pathology, Singapore General Hospital, Singapore

Abstract

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma and is derived from thyroid follicular cells. In contrast, medullary thyroid carcinoma (MTC) is rare and originates from the parafollicular C-cells. Synchronous occurrence of these two carcinomas is uncommon and occurs as either discrete lesions or as a mixed lesion. The current case report describes a 50-year-old woman with synchronous multiple discrete MTC and PTC with lymph nodes metastasis. Pathologists and treating physicians should be aware of the synchronous coexistence of these entities to avoid possible misdiagnosis.

Keywords: endocrine pathology, thyroid cancer, medullary thyroid carcinoma, papillary thyroid carcinoma

INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma and is derived from thyroid follicular cells. In contrast, medullary thyroid carcinoma (MTC) is rare and originates from the parafollicular C-cells, which is commonly thought to be derived from the neural crest via the ultimobranchial body. However, new studies have shown that parafollicular C-cells may share an endodermal origin with thyroid follicular cells. Synchronous occurrence of these two carcinomas is uncommon and occurs in two forms: first as discrete MTC and PTC separated by normal thyroid tissue and secondly as a mixed medullary and follicular-derived thyroid carcinoma, in which single or multiple lesions demonstrate morphology and immunoreactivity for both MTC and follicular derived carcinoma, including PTC. Although slightly more than 100 cases of concurrent PTC and MTC have been reported, this is the fourth case of synchronous multiple foci of both MTC and PTC reported in the English literature. We aim to describe a case report of this rare entity, give a short review of the literature and emphasize the role of the pathologist in identifying this rare occurrence.

CASE REPORT

A 50-year-old Chinese woman with no known family history of endocrine disorder or any previous external radiation therapy was referred to our hospital for multinodular goitre evaluation. Ultrasound assessment showed multiple nodules in the left and right lobes ranging from 0.7 to 2.5 cm in maximum dimension. No enlarged or abnormal cervical lymph nodes were identified. Ultrasound-guided FNA of a right midpole nodule showed cellular smears interpreted as follicular epithelial cells arranged in loose clusters and singly dispersed with mild nuclear atypia in a background of blood and admixed colloid, suggestive of follicular lesion (Fig.1). Some of these cells showed eccentric nuclei, nuclear binucleation, uniform nuclei with occasional enlarged nuclei and fine chromatin distribution. Initially, a right hemithyroidectomy was performed, followed by completion thyroidectomy after histological diagnosis of malignancy. Neck dissection was not performed. On macroscopic examination, the right lobe revealed multiple yellow-whitish nodules in the middle lobe ranging from 0.5cm to 1cm in maximum dimension. A well-circumscribed and encapsulated brown nodule was also present in the right lower lobe measuring 1.3 x 1.1 x 1 cm. Examination of the...
left completion thyroidectomy demonstrated a small white nodule measuring 0.3 cm in maximum dimension at the superior tip of the pyramidal lobe and a colloid nodule measuring 0.6 cm in maximum dimension at the isthmus. No gross lesion was seen upon sectioning of the left lobe.

Microscopic examination of the total thyroidectomy showed several nests of MTC with uniform round nuclei, fine stippled chromatin and ample granular cytoplasm (Fig. 2) in the right lobe, with the largest lesion measuring 0.3 cm in maximum dimension at the superior tip of the pyramidal lobe and a colloid nodule measuring 0.6 cm in maximum dimension at the isthmus.

FIG. 1: Ultrasound-guided FNA of the 0.7 cm right midpole nodule showed cellular smears composed of follicular epithelial cells arranged in loose clusters and were mostly singly dispersed with mild nuclear atypia in a background of blood and admixed colloid, suggestive of follicular lesion. (A) DQ stain at x10 magnification. (B) Pap stain at x40 magnification

FIG. 2: Medullary thyroid carcinoma composed of several solid nests of epithelial cells with neuroendocrine cytological features, including uniform round nuclei, fine stippled chromatin and ample granular cytoplasm (A) H&E at x10 magnification. These cells are positive for (B) calcitonin, (C) mCEA and (D) TTF1
FIG. 3: Papillary thyroid carcinoma, demonstrating nuclear clearing, grooves and nuclear pseudoinclusions (A) H&E at x10 magnification. These cells are negative for (B) calcitonin and (C) mCEA and are positive for (D) TTF1

0.8cm in maximum dimension. The tumour cells were positive for calcitonin. No background C-cell hyperplasia was identified. There was a separate PTC (1.3 cm) (Fig. 3) in the right lobe and a papillary thyroid microcarcinoma (PTMC) (0.1 cm) in the left lobe, composed of papillary structures lined by cells with nuclear clearing, nuclear grooves, intranuclear cytoplasmic pseudoinclusions and overlapping nuclei. These cells were positive for TTF1 and negative for calcitonin and mCEA. Two prelaryngeal lymph nodes with metastatic MTC were also noted. The final diagnosis rendered was that of a synchronous multifocal MTC and PTC (Fig. 4).

DISCUSSION

There are many proposed views as to how two carcinomas may concurrently occur in the same patient. The most commonly held view is that it occurs as a coincidence, as there is a high incidence of PTMC in the general population. This is in view of the fact that most of the papillary components in such cases are microcarcinomas (77%). As there is a high incidence of PTMC in the general population, it is suggested that the PTMC may coincidentally occur in a patient with MTC. However, in this case report, it is the MTC component that is less than 1 cm in maximum dimension, whereas the

FIG. 4: Diagram of lesions’ distribution within the thyroid lobes. MTC, Medullary thyroid carcinoma; PTC, Papillary thyroid carcinoma; PTMC, Papillary thyroid microcarcinoma
PTC component is more than 1cm in maximum dimension.

Other possible hypotheses for the synchronous occurrence include involvement of the RET proto-oncogene in both PTC and MTC, whether by a point mutation (in MTC) or gene rearrangement (in PTC). However, only a few cases of synchronous MTC and PTC had molecular analyses performed, of which only one case of somatic RET mutation was reported with most of the rest of the MTC cases demonstrating germline RET mutation. All the PTC tissue were positive for BRAF (Val600Glu) mutation but negative for RET/PTC. Hence, it is more likely that the MTC was caused by a germline RET mutation and the PTC was caused by a somatic BRAF mutation, arguing against the role of a single RET mutation in the genesis of this synchronous occurrence.

Regardless of the pathogenesis, it is important for the pathologist to be aware of its existence. This is especially important as the histologic appearance of both MTC and PTC can be quite variable and difficult to differentiate, especially by a general pathologist who may not have had much experience with thyroid malignancies. Cytological and architectural features such as fine salt-and-pepper chromatin and round to spindle cells with granular cytoplasm should alert one to consider MTC versus the optically-clear nuclei with nuclear grooves and pseudoinclusions of a PTC. Moreover, the cytology of medullary carcinoma may be indistinguishable from that of a follicular lesion, as in this case (Fig. 1). With small suspicious foci which may be difficult to identify, one should not hesitate to perform calcitonin immunohistochemical staining to confirm or exclude MTC, despite a definite PTC component within the thyroid. The management of these two carcinomas differs, with PTC possibly requiring radioactive iodine treatment in addition to surgery and surgical treatment for MTC routinely followed by postoperative serum calcitonin levels to assess the presence of residual disease. In our case, the patient was followed up with regular thyroid ultrasound and serum calcitonin levels.

In addition, both PTC and MTC components are prone to lymph node metastasis, and may metastasize as MTC and/or PTC. On occasions, pathologists receive lymph nodes for histological/cytological analysis in a patient with a past history of uncertain or misdiagnosed thyroid malignancy. It is thus important to be aware that synchronous tumours do occur.

In summary, we present a case report of synchronous discrete MTC and PTC. Pathologists and treating physicians should be aware of this possibility to avoid possible misdiagnosis and subsequent mismanagement.

REFERENCES