Synchronous papillary-medullary thyroid microcarcinoma: a case report

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Background: Papillary thyroid carcinoma is the most common type of thyroid carcinoma, making up 85–90% of all thyroid carcinomas. Medullary thyroid carcinoma is the third most common type of thyroid carcinoma, making up less than 5% of all thyroid carcinomas. However, synchronous papillary-medullary thyroid carcinoma is exceedingly rare and has not been well described historically. There have been fewer than 40 cases reported in the current literature.

Case Description: In this case report we present a 65-year-old man with synchronous papillary-medullary thyroid carcinoma. A 65-year-old man presented with a symptomatic multinodular thyroid goiter. Ultrasound (US) confirmed bilateral thyroid nodules, and he was initially managed nonoperatively. Fine needle aspiration (FNA) biopsy of the left dominant nodule revealed atypia of undetermined significance (AUS) (Bethesda class III). Further assessment of the FNA specimen with ThyGeNEXT® (mutation panel) revealed no mutations and the ThyraMIR® (microRNA risk classifier) was negative, which classified the results as very highly likely to be benign. Due to worsening local compressive symptoms, a total thyroidectomy was performed. Final surgical pathology revealed incidental multicentric, multifocal micropapillary carcinoma foci from (0.1 to 0.5 cm), and a 0.3 cm medullary carcinoma in the left thyroid lobe on the background of nodular hyperplasia.

Conclusions: Synchronous papillary-medullary thyroid carcinoma is a rare finding that should be considered in patients with symptomatic multinodular thyroid goiters. It is important to report this case to increase awareness and improve our understanding and management of these unusual carcinomas in the future.

Keywords: Papillary; medullary; carcinoma; case report

Received: 06 February 2022; Accepted: 24 June 2022; Published: 25 July 2022.
doi: 10.21037/acr-22-13
View this article at: https://dx.doi.org/10.21037/acr-22-13

Introduction

The most common type of thyroid carcinoma is papillary thyroid carcinoma, comprising 85–90% of all thyroid carcinomas (1). Medullary thyroid carcinoma, originating from calcitonin-producing parafollicular cells (C-cells), is the third most common type of thyroid carcinoma. It makes up less than 5% of all thyroid carcinomas (1). The micro subtypes of thyroid carcinomas are defined as carcinomas measuring 1 cm or less. Although both papillary and medullary thyroid carcinomas have been well studied in isolation, our knowledge regarding the biology, natural history, and treatment of synchronous papillary-medullary thyroid carcinoma is limited and can pose both diagnostic and management challenges. Here we present a rare case of synchronous papillary-medullary thyroid microcarcinoma and treatment via total thyroidectomy, radioactive iodine

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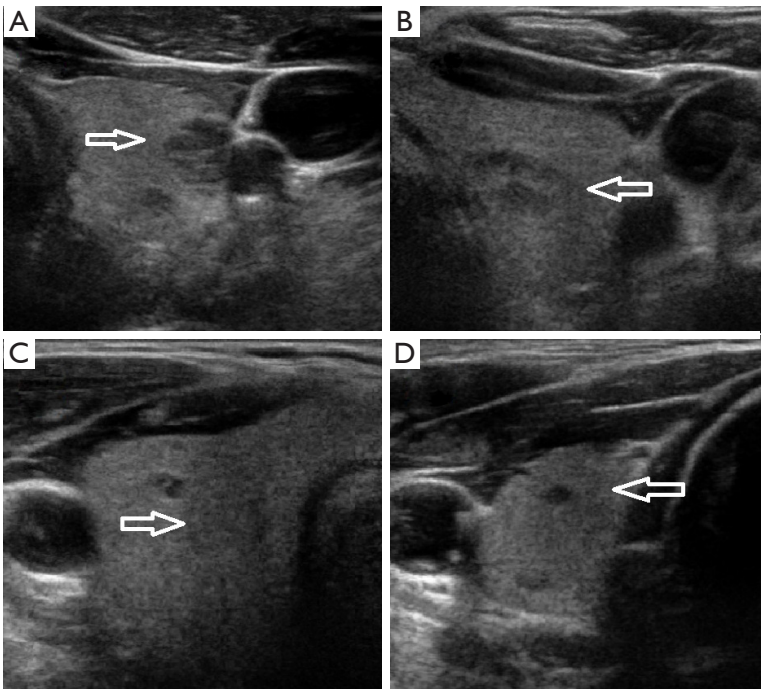

Figure 1 US images of the patient's thyroid gland. (A,B) Transverse US views of the left thyroid lobe with arrows pointing at multiple nodules. (C,D) Transverse US views of the right superior and mid thyroid lobe with arrows pointing at multiple nodules. US, ultrasound.

ablation, and exogenous hormonal suppression. We present the following case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-22-13/rc).

Case presentation

A 65-year-old man presented with an increasingly symptomatic multinodular thyroid goiter that had progressed over the course of years. The patient denied a history of radiation exposure but had a family history of an unknown type of thyroid carcinoma in his mother. Ultrasound (US) examination of the goiter confirmed bilateral thyroid nodules up to ~1.6 cm (*Figure 1*). Fine needle aspiration (FNA) biopsy of the left dominant nodule showed atypia of undetermined significance (AUS) (Bethesda class III) with atypical microfollicles and follicular cells with nuclear grooves and clearing. He had no mutations detected by the ThyGeNEXT oncogene panel and the ThyraMIR® (microRNA risk classifier) was negative, which then classified the FNA results as very highly likely benign. Because of the progressively worsening local, compressive symptoms after his FNA, the patient underwent a successful total thyroidectomy with intraoperative nerve integrity monitoring. He had an uneventful postoperative recovery course with preserved phonation and parathyroid gland function. The final surgical pathology report indicated a synchronous multicentric multifocal papillary microcarcinoma and medullary microcarcinoma. Pathology analysis showed a multifocal classic papillary microcarcinoma, mpT1aNx [American Joint Committee on Cancer (AJCC)], with two foci in the left lobe (0.2 and 0.1 cm) and two foci in the right lobe (0.1 and 0.5 cm). There was also a unifocal medullary carcinoma, AJCC pT1aNx, 0.3 cm in the left lobe (*Figure 2*). The specimen showed no extrathyroidal extension, angioinvasion, or lymphovascular invasion. The margins were uninvolved based on the total thyroidectomy specimen. The patient underwent a postoperative radioactive iodine ablation with 30 miCu of radioactivity and was placed on a suppressive dose of exogenous thyroid hormone (levothyroxine). On follow-up 6 months postoperatively, the patient is doing well, disease free with a thyroglobulin level less than 0.1 ng/mL and a calcitonin level less than 2 ng/mL.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as

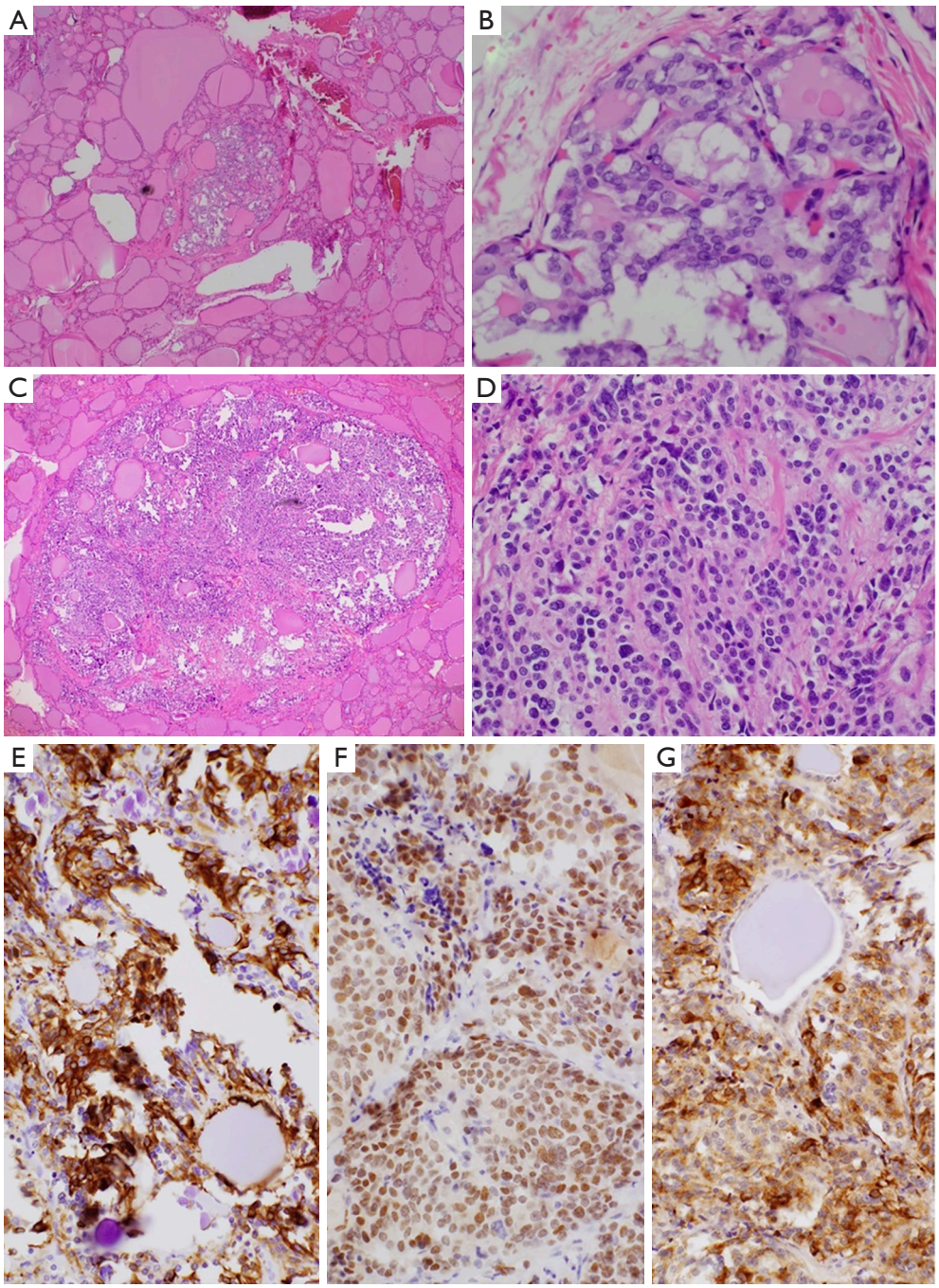

Figure 2 Various staining images of components of the synchronous papillary-medullary thyroid microcarcinoma. (A) Low power (40×) and (B) high power (100×) H&E histological images of infiltrative neoplasm with well developed nuclear features of PTC, follicular variant represented by multiple discreet nodules with follicular cells exhibiting nuclear enlargement, elongation and overlapping, chromatin clearing, irregular nuclear contour, nuclear grooves and nuclear pseudoinclusions. (C) Low power (40×) and (D) high power (100×) H&E histological images of MTC represented by a well circumscribed nodule with round to polygonal cells in nests, cords or follicles. Eosinophilic to amphophilic granular cytoplasm. Round centrally located nuclei with coarse chromatin and no nuclear features of PTC. Immunohistochemistry images of MTC represented by (E) strong staining for calcitonin, (F) weak to moderate staining for TTF-1, and (G) strong staining for CK7. H&E, hematoxylin and eosin; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; TTF-1, thyroid transcription factor-1; CK7, cytokeratin 7.

revised in 2013). 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 editorial office of this journal.

Discussion

Thyroid follicular structures mainly consist of two cell populations: follicular cells which produce colloid and thyroid hormones, and parafollicular cells which produce calcitonin. Follicular cells can give rise to a spectrum of carcinomas ranging from well-differentiated papillary carcinoma to undifferentiated anaplastic thyroid carcinoma. The prognostically-favorable papillary carcinoma has a greater than 99% 10-year survival rate in people 45 years and younger regardless of the stage of the disease (2). On the other hand, anaplastic thyroid carcinoma carries a very poor prognosis with a median survival rate of 4 months (3). Parafollicular cells are neuroendocrine cells that originate from the pharyngeal endoderm and can give rise to medullary carcinoma. Medullary carcinoma can arise sporadically or as part of a familial multiple endocrine neoplasia (MEN) such as MEN 2A, and MEN 2B.

Rarely, two different types of carcinomas can co-occur, such as papillary carcinoma and medullary carcinoma, classified as a synchronous (mixed) papillary-medullary thyroid carcinoma. The literature shows that mixed tumors are most often coalesced in the same tumor bulk (*Table 1*). This case is very specific, because we describe completely separate synchronous papillary and medullary carcinomas. The origin and biology of synchronous papillary-medullary thyroid carcinomas are not completely understood; however, leading theories include stem cell theory, collision effect theory, and hostage theory (27,28). The stem cell theory suggests that the carcinoma originates from a rare population of cancerous stem cells (29). Collision effect theory postulates that the mixed carcinoma originates as two distinct tumor types that initiate near each other resulting in a polyclonal neoplasm that is recognized as a single entity (27). The "hostage" theory hypothesizes that the carcinoma is a result of adenomatous areas being sequestered by a different type of tumor (28).

Thyroid carcinomas can be diagnosed in a few different ways, the main ones are physical exam with imaging for confirmation or incidental finding on an US, magnetic resonance imaging (MRI), or computed tomography (CT) scan. Depending on the index of suspicion, thyroid nodules should be biopsied using FNA. For medullary carcinomas calcitonin levels should be assessed. If biopsy reveals medullary carcinoma a priori, then it must be staged due to a high probability of metastasis to the locoregional lymph nodes, lungs, bones, brain. Metastatic disease should be suspected if the calcitonin level is greater than 500 pmol/L (30). Diagnosis is most often made by morphological examination, standard immunohistochemistry studies, and molecular detection based on the biopsy sample. Other diagnostic hints indicating this disease include elevated laboratory values of thyroglobulin, calcitonin, and carcinoembryonic antigen (4,5,9,10,14,17,31).

In this case, the diagnosis was made post-surgically. The patient's FNA biopsy revealed AUS. Total thyroidectomy was the choice of treatment due to the enlarging goiter with progressively worsening local compressive symptoms. The final surgical pathology report indicated a synchronous multicentric multifocal papillary microcarcinoma and medullary microcarcinoma.

The medullary component is the main prognostic factor in cases of synchronous papillary-medullary thyroid malignancy, and the extent of surgical resection depends on the stage of the tumor (4,5,7,10,32). Although radioactive iodine ablation and thyroid-stimulating hormone (TSH) suppression is not useful in treatment of lone medullary thyroid carcinoma due to lack of accumulation of radioiodine in parafollicular C-cells, it may be useful for the treatment of the co-occurring papillary carcinoma (1,33). In our case, the incidentally found tumors were treated appropriately with simple total thyroidectomy due to the lack of clinically significant lateral neck lymphadenopathy, post-surgical radioactive iodine ablation, and suppressive levels of oral levothyroxine. In addition, the patient will be followed annually with TSH, thyroglobulin, and calcitonin levels to monitor for recurrence, with further imaging if lab results warrant suspicion. Our case follows the management guidelines laid out by the Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma (33).

Synchronous papillary-medullary thyroid microcarcinoma is a rare co-incidental carcinoma that should be treated according to the staging of its components. Although papillary thyroid carcinoma is amenable to radioactive iodine ablation, medullary thyroid carcinoma is not, and therefore synchronous papillary-medullary thyroid microcarcinoma should be treated surgically to reduce the risk of recurrence. They also have different biological effects as the papillary form is derived from thyroid hormone-producing follicular cells, whereas the medullary form is derived from C-cells. The downstream effects can then be used to observe

Table 1 Published cases

Article number	Citation	Number of cases	Histology of thyroid components
1	Nangue *et al.*, 2009 (4)	1	MTC in the right thyroid lobe, closely intermingled with a nonencapsulated classical PTC
2	Samarasinghe *et al.*, 2020 (5)	1	Multifocal PTC in the left thyroid nodule. MTC and PTC within a lymph node of left lateral neck. MTC in the right lobe
3	Gurkan *et al.*, 2014 (6)	2	Mixed medullary-papillary thyroid carcinoma with co-occurrence of MTC and PTC
4	Yao *et al.*, 2020 (7)	1	PTC in the right lobe and isthmus of the thyroid. MTC in the left lobe
5	Hasney *et al.*, 2010 (8)	1	MTC with a distinct focus of PTC in the left lobe of the thyroid
6	Jain *et al.*, 2014 (9)	1	Mixed medullary-papillary carcinoma of the thyroid
7	Myoteri *et al.*, 2016 (10)	1	Mixed MTC/PTC
8	Guerreiro *et al.*, 2021 (11)	1	Mixed medullary-papillary carcinoma of the thyroid
9	Shimizu *et al.*, 2000 (12)	1	Mixed medullary-follicular carcinoma of the thyroid and PTC with a clear border between the two components
10	Chambers *et al.*, 2021 (13)	1	PTC which transitioned to a morphologically and immunophenotypically distinct MTC component within the same lesion
11	Kataria *et al.*, 2013 (14)	1	Mixed medullary-papillary carcinoma of the thyroid with C-cell hyperplasia
12	Tang *et al.*, 2017 (15)	1	Synchronous multiple discrete MTC and PTC
13	Wu *et al.*, 1998 (16)	1	Mixed medullary-follicular carcinoma of the thyroid with concurrent PTC
14	Shiroko *et al.*, 2001 (17)	1	Mixed medullary-papillary carcinoma in right thyroid
15	Parker *et al.*, 1985 (18)	1	Medullary, papillary, follicular, and undifferentiated carcinoma of the same gland
16	Dionigi *et al.*, 2007 (19)	2	Multicentric MTC and PTC with mixed features found in the isthmus of the gland
17	Lax *et al.*, 1994 (20)	3	In two cases the papillary component was characterized by typical papillae with a fibrovascular core; in one a follicular variant of PTC was found
18	Macák *et al.*, 1997 (21)	1	MTC in the upper part of the right lobe and mixed medullary-papillary carcinoma in the left lobe of the thyroid gland
19	Seki *et al.*, 2004 (22)	2	MTC and PTC separate but synchronous in the thyroid but mixed in some lymph node metastases
20	Michal *et al.*, 1993 (23)	2	Mixed medullary-follicular carcinoma with cytological features of PTC
21	Gupta, 2013 (24)	1	Parathyroid hyperplasia and MTC mixed with PTC
22	Meshikhes *et al.*, 2004 (25)	1	PTC in the right lobe and MTC in the left lobe
23	Apel *et al.*, 1994 (26)	1	Thyroglobulin-positive PTC intermixed with calcitonin-containing MTC

MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

for recurrence by monitoring calcitonin, TSH, and thyroglobulin.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-22-13/rc

Peer Review File: Available at https://acr.amegroups.com/

article/view/10.21037/acr-22-13/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-22-13/coif). VKN serves as an unpaid editorial board member of *AME Case Reports* from February 2022 to January 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

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doi: 10.21037/acr-22-13
Cite this article as: Medam RR, Castro G, Alhassan R, Neychev VK. Synchronous papillary-medullary thyroid microcarcinoma: a case report. AME Case Rep 2022;6:27.