

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,400

Open access books available

133,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Calcitonin Expression in the Metastatic Tissue of Medullary Thyroid Carcinoma

Wei-Wen Hung, Kun-Bow Tsai and Pi-Jung Hsiao

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/51959>

1. Introduction

Medullary thyroid carcinoma (MTC) is an uncommon primary thyroid carcinoma accounting for as much as 10% of all thyroid malignancies and as much as 14% of thyroid cancer-related deaths.[1] It is a neuroendocrine malignancy arising from the C cell or parafollicular cell of the thyroid.[2] The sporadic and hereditary forms of MTC account for 80% and 20% of all cases, respectively.[3] The hereditary form is part of the multiple endocrine neoplasia (MEN) syndromes including MEN 2A (MTC, pheochromocytoma, and hyperparathyroidism), MEN 2B (MTC, pheochromocytoma, mucosal neuroma, and marfanoid habitus), and familial MTC (FMTC).[4] About 40% to 50% of sporadic MTC cases present with distant metastasis involving cervical lymph nodes, lungs, liver, and/or bones at initial diagnosis.[5] The literature reports other rare metastatic sites including pituitary metastasis, [6] choroidal and optic disc metastasis, [7,8] breast metastasis, [9] and skin metastasis. [10]

Certain diagnostic tools such as calcitonin and Rearranged during Transfection (RET) proto-oncogene tests enable the discovery of hereditary MTC cases in the preclinical stage, allowing for early surgical interventions and resulting in high cure rates. [5] In contrast to hereditary MTC, early detection of sporadic MTC is difficult, making prognosis more unfavorable. [11] The initial presentation of a metastatic tumor may be difficult to diagnose if the clinician is unaware of the occult primary thyroid cancer. Immunohistochemical staining with calcitonin for the metastatic tumor has been used as a diagnostic marker for MTC. [12] However, no consensus exists regarding calcitonin expression by metastatic MTC tissues. Still calcitonin staining is routinely used to make a differential diagnosis of MTC. This poses particular challenges when metastatic MTC occurs without the expression of calcitonin.

We had encountered a case of sporadic MTC in a 73-year-old man who initially presented with two ill-defined pulmonary opacities on chest radiography (CXR). Computed tomography (CT) of the chest inadvertently found a thyroid nodule, which led to the ultimate diagnosis of primary MTC with pulmonary metastasis. This atypical histopathologic presentation of pulmonary metastasis from MTC made diagnosis particularly challenging.

2. Body

The patient was a 73-year-old man with an unremarkable medical history. He had the initial presentation of intermittent anterior chest pain for more than 20 days. The CXR showed two ill-defined opacities in the upper lobe and the hilum of the right lung (Figure 1B). Chest CT findings highly suggested bronchogenic carcinoma localized in the upper and middle lobes of the right lung with extension and encasement to the adjacent hilum and the segmental bronchus of right upper lobe (Figure 1A). We discovered lymph node metastases to the right anterior mediastinum and subcarinal region and an accidental thyroid nodule over the right lobe. Initial pathological examination of a transbronchoscopic lung biopsy favored poorly-differentiated carcinoma with desmoplastic stroma infiltrated by sheets of cancer cells that had hyperchromatic nuclei with no distinct nucleoli (Figure 2A, x40).

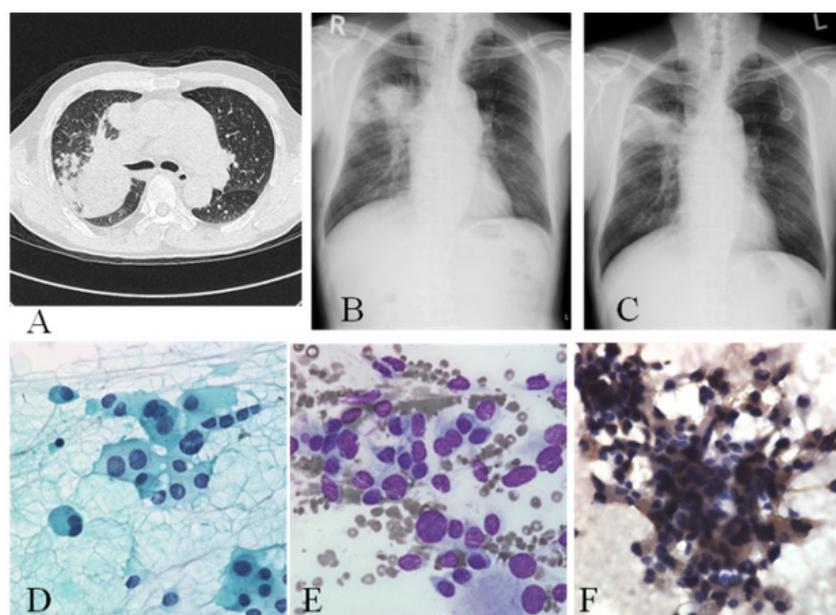


Figure 1. (A) chest CT at diagnosis: highly suggested bronchogenic carcinoma (B) chest PA at diagnosis: two ill-defined opacities over the right upper lobe and the right hilum of the lung (C) chest PA after chemotherapy: partial shrinkage of the tumor opacity. Thyroid aspiration (x100 objective lens) with (D) Papanicolaou's stain: dispersed cell pattern with nuclear eccentricity and "salt-and-pepper" chromatin (E) Riu's stain: plasmacytoid cells with binucleation and basophilic stippling in the cytoplasm (F) positive calcitonin stain using liquid-based cytology (LBC) method

Sonography revealed a calcified heterogenous right thyroid tumor greatest diameter 2.9cm. Fine-needle aspiration cytology with Papanicolaou's stain showed cells arranged in

dispersed pattern with nuclear eccentricity and “salt-and-pepper” chromatin (Figure 1D, x100). Characteristic plasmacytoid cells with binucleation and basophilic stippling in the cytoplasm were also noted in the aspiration cytology with Riu’s stain (Figure 1E, x100). MTC was highly suspected because there was a positive immunocytochemical staining for calcitonin as detected by liquid-based cytology (LBC) with Ligui-Prep™ (LGM International, Fort Lauderdale) (Figure 1F, x100), and because serum calcitonin level was above 950 pg/ml (normal range: 0-42 pg/ml) and carcinoembryonic antigen (CEA) level at 259 ng/ml (normal range: 0-3 ng/ml).

After total thyroidectomy, the diagnosis of MTC was confirmed by positive immunohistochemical staining for chromogranin-A (Figure 2F, x40), synaptophysin (Figure 2G, x40), calcitonin (Figure 2H, x40), and Congo-red stain for amyloid. Because of the similarity between the histopathologic patterns of focal vascular invasions in the thyroid (Figure 2E, x40) and the lung carcinoma (Figure 2A, x40), MTC metastasis to the lung was further diagnosed based on a positive finding of chromogranin-A (Figure 2B, x40) and synaptophysin (Figure 2C, x40), though there was no staining of calcitonin (Figure 2D, x40).

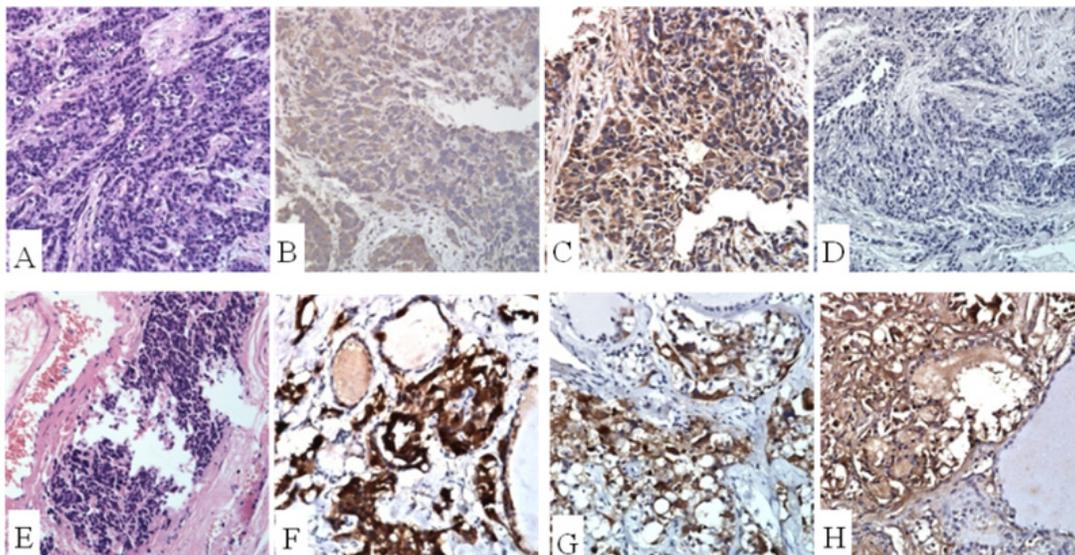


Figure 2. (x40 objective lens) Lung sections staining with H.E. (A) showing poorly-differentiated cancer cells infiltrating in desmoplastic stroma, with strong expressions for chromogranin-A (B) and synaptophysin (C), but negative calcitonin (D). Thyroid sections staining with H.E. (E) showing focal vascular invasions in the thyroid with poorly-differentiated cancer cell morphology resembling that in the lung section, with positive expressions for chromogranin – A (F), synaptophysin (G), and calcitonin (H).

Because the patient had no family history of MTC and no evidence of pheochromocytoma and hyperparathyroidism, he was diagnosed with sporadic MTC. As for the treatment, post-operation chemotherapy with Gemcitabine was administered to treat pulmonary metastasis of the MTC. After total thyroidectomy and one course of gemcitabine, serum CEA and calcitonin levels decreased to 135 ng/ml and 766.7 pg/ml, respectively. CXR showed partial shrinkage of the tumor opacity (Figure 1C).

To our knowledge, this is the first reported case of accidental MTC initially presenting as pulmonary metastasis without calcitonin expression in the metastatic lesions. A correct diagnosis might have been missed if the thyroid nodule had not been discovered. The atypical histopathologic patterns in this MTC case could have led to a misdiagnosis of double cancer.

We presented this case with several issues worth discussing. First, the absence of calcitonin expression in the pulmonary metastases in our case did not exclude the possibility of primary MTC. Calcitonin has been recognized as a specific and sensitive tumor marker for MTC. Although the disparity between tissue and serum calcitonin in patient with medullary thyroid carcinoma were reported, [13] the follow-up of patients with MTC before and after total thyroidectomy by the measurement of calcitonin is still widely used in clinical condition. Calcitonin is a small polypeptide hormone of 32 amino acids that is produced almost exclusively by neuroendocrine C cells in the thyroid. [14] However, little was known about the calcitonin expression in the metastatic tissue of MTC. Only four of 142 MTC cases in a retrospective study were described as “atypical”, characterized by cytomorphic features and positive neuroendocrine markers of chromogranins and synaptophysin. Among the four cases, three had very little expression of calcitonin and one had no expression of this tumor marker. [15] Previous reports have also postulated that the metastatic lesion may lose the ability to express calcitonin, [12] which is consistent with the patient in this report who exhibited poorly differentiated cancer cell morphology (Figure 2A, x40) similar to that seen in the focal vascular invasion of thyroid (Figure 2E, x40). The pathological mechanisms of the poorly-differentiated MTC cells without calcitonin expression are not well understood. Oncocytic variant of MTC seen in the recurrent tumor has been documented in the literature to represent a further step in tumor progression and may be indicative of a poor prognosis. [16] But regarding the absence of calcitonin expression in the metastatic tissue of MTC, no references have been found. Thus we postulated two possible mechanisms for the absence of calcitonin expression in the metastatic tissue of medullary thyroid carcinoma: the first one is that the potential for metastasis increases as cancer cells lose their ability to secrete calcitonin during dedifferentiation, and the second explanation is that the secondary environment (metastatic site) may have disabled the cancer cells’ ability to secrete calcitonin. Further research will be needed to elucidate the exact mechanism.

Second, the radiographic patterns of pulmonary metastasis from MTC in this patient were hard to differentiate from primary lung carcinoma. The patient presented with elevated serum CEA level and two ill-defined pulmonary opacities in the right upper lobe and the right hilum, which clinically resembled primary lung carcinoma. Pulmonary metastases from MTC generally exhibit a macronodular, or “cannonball” appearance with clear-cut margins.[17] Reticulonodular perihilar lesions,[17] calcified pulmonary metastases,[18] and micronodular patterns[17] have also been reported in the literature. The diverse radiographic manifestations of pulmonary MTC metastases pose as a diagnostic challenge for clinicians. Because 40% to 50% of sporadic MTC cases are initially discovered through

distant metastasis,[5] the clinician may need to test the patient's serum calcitonin level to rule out MTC if a thyroid nodule and a pulmonary lesion coexist. We believe that immunohistochemical staining with neuroendocrine markers (chromogranin and synaptophysin) are more useful than calcitonin expression for testing transbronchoscopic lung biopsy specimens, even if elevated serum CEA may favor the possibility of lung (adeno)carcinoma. In addition to calcitonin, CEA can be secreted and released by the malignant transformed C cells. Although CEA is not specific for the diagnosis of MTC, as its levels can be elevated in several types of tumors, the serum levels of CEA is an excellent test for monitoring disease progression once the diagnosis of MTC has been confirmed. [14]

In our case, liquid-based cytology (LBC) was particularly helpful in facilitating immunocytochemical staining. Although most MTC can be easily diagnosed based on cytomorphologic findings in aspirates with Pap-staining[12,19] or Riu's stain,[20,21] calcitonin staining has been regarded as the gold standard for the definitive diagnosis of MTC.[12] LBC allows ancillary tests, including immunocytochemical staining, to be conducted on residual cell samples.[22] To our knowledge, this is the first reported case of a primary thyroid carcinoma confirmed by LBC. Although cervical smear using LBC preparation has been described,[23] the role of LBC in thyroid aspiration cytology has yet to be explored. We expect the clinical application of LBC in thyroid fine needle aspiration cytology to help in establishing correct preoperative diagnoses.

The five-year and ten-year survival rates of MTC with distant metastasis have been estimated at 60% and 40%, respectively.[24] Cancer staging of MTC at initial diagnosis is highly predictive of future mortality in long-term follow-up.[25] Radioactive iodine, external beam radiation therapy, and conventional chemotherapy have not resulted in satisfactory response in metastatic MTC.[26] Combination chemotherapy regimens used to treat metastatic MTC, including doxorubicin, cisplatin, fluorouracil, dacarbazine, streptozocin, cyclophosphamide, and vincristine have yielded limited outcomes with tumor response rates less than 20%.[27] Gemcitabine, a pyrimidine antimetabolite, has not been described in the literature as a treatment for MTC.[27] Based on an *in vitro* study in which gemcitabine inhibited proliferation and neuroendocrine activity of human TT cells derived from MTC,[28] we used gemcitabine to treat the pulmonary metastasis of MTC in this patient. This is the first case report demonstrating partial response to gemcitabine in a patient with pulmonary metastasis of MTC.

3. Conclusion

In conclusion, metastatic medullary thyroid carcinoma with atypical chest radiography and calcitonin-free histopathologic lung lesions can be difficult to diagnose. This unique case report demonstrates that MTC metastatic lesions may not express its routine biomarker, calcitonin.

Author details

Wei-Wen Hung and Pi-Jung Hsiao

*Division of Endocrinology and Metabolism, Department of Internal Medicine,
Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*

Kun-Bow Tsai

*Department of Pathology, Kaohsiung Municipal Hsiao-Kang Hospital,
Kaohsiung Medical University, Kaohsiung, Taiwan*

Acknowledgement

The authors thank Min-Jan Tsai, Wan-Chen Hsieh, Ya-Chun Tseng in Kaohsiung Municipal Hsiao-Kang Hospital for their assistances with the immunocytochemical and immunohistochemical studies

4. References

- [1] Roman S, Lin R, Sosa JA (2006) Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1252 cases. *Cancer*. 107 (9): 2134-42.
- [2] Kebebew E, Ituarte PH, Siperstein AE, Duh QY, Clark OH (2000) Medullary thyroid carcinoma: clinical characteristics, treatment, prognostic factors, and a comparison of staging systems. *Cancer*. 88 (5): 1139-48.
- [3] Lewis CE, Yeh MW (2008) Inherited endocrinopathies: an update. *Mol Genet Metab*. 94 (3): 271-82.
- [4] Fialkowski EA, Moley JF (2006) Current approaches to medullary thyroid carcinoma, sporadic and familial. *J Surg Oncol*. 94 (8): 737-47.
- [5] Martins RG, Rajendran JG, Capell P, Byrd DR, Mankoff DA (2006) Medullary thyroid cancer: options for systemic therapy of metastatic disease? *J Clin Oncol*. 24 (11): 1653-5.
- [6] Bhatoe HS, Badwal S, Dutta V, Kannan N (2008) Pituitary metastasis from medullary carcinoma of thyroid: case report and review of literature. *J Neurooncol*. 89 (1): 63-7.
- [7] Bianciotto CG, Demirci HY, Shields CL, Shields JA (2008) Simultaneous eyelid and choroidal metastases 36 years after diagnosis of medullary thyroid carcinoma. *Ophthal Plast Reconstr Surg*. 24 (1): 62-3.
- [8] Yildiz I, Sen F, Tuncer S, Kilic L, Basaran M, Bavbek S (2011) Optic disc and choroidal metastasis from sporadic medullary thyroid carcinoma: case report and review of the literature. *Onkologie*. 34 (11): 630-3.
- [9] Nofech-Mozes S, Mackenzie R, Kahn HJ, Ehrlich L, Raphael SJ (2008) Breast metastasis by medullary thyroid carcinoma detected by FDG positron emission tomography. *Ann Diagn Pathol*. 12 (1): 67-71.
- [10] Sanii S, Tavangar SM (2011) Cutaneous metastasis of medullary thyroid carcinoma as the initial manifestation of an otherwise limited malignancy: a case report. *Am J Dermatopathol*. 33 (7): 716-8.

- [11] Bergholm U, Bergstrom R, Ekblom A (1997) Long-term follow-up of patients with medullary carcinoma of the thyroid. *Cancer*. 79 (1): 132-8.
- [12] Bhanot P, Yang J, Schnadig VJ, Logrono R (2007) Role of FNA cytology and immunochemistry in the diagnosis and management of medullary thyroid carcinoma: report of six cases and review of the literature. *Diagn Cytopathol*. 35 (5): 285-92.
- [13] Alapat DV, Ain KB, Sloan DA, Monaghan KG, Karabakhtsian RG (2011) Disparity between tissue and serum calcitonin and carcinoembryonic antigen in a patient with medullary thyroid carcinoma. *Endocrine*. 39 (2): 148-52.
- [14] Elisei R, Pinchera A (2012) Advances in the follow-up of differentiated or medullary thyroid cancer. *Nat Rev Endocrinol*. 8(8): 466-75.
- [15] Schmid KW, Ensinger C (1998) Atypical" medullary thyroid carcinoma with little or no calcitonin expression. *Virchows Arch*. 433 (3): 209-15.
- [16] Tranchida P, Estigarribia J, Sethi S, Giorgadze T (2011) Cytologic diagnosis of recurrent medullary thyroid carcinoma with oncocytic change twenty-one years post-thyroidectomy: case report and review of the literature. *Diagn Cytopathol*. 39 (9): 641-6.
- [17] Afshar K, Alalawi R, Boylen CT (2007) Micronodular radiographic pulmonary pattern in metastatic medullary thyroid carcinoma. *J Natl Med Assoc*. 99 (5): 575-7.
- [18] Jimenez JM, Casey SO, Citron M, Khan A (1995) Calcified pulmonary metastases from medullary carcinoma of the thyroid. *Comput Med Imaging Graph*. 19 (4): 325-8.
- [19] Green I, Ali SZ, Allen EA, Zakowski MF (1997) A spectrum of cytomorphologic variations in medullary thyroid carcinoma. Fine-needle aspiration findings in 19 cases. *Cancer*. 81 (1): 40-4.
- [20] Tsou MH, Lin HH, Ko JS (1997) Riu's stain and the cytologic diagnosis of thyroid fine-needle aspiration: a single cancer center experience. *Diagn Cytopathol*. 16 (6): 543-7.
- [21] Hsieh MH, Hsiao YL, Chang TC (2007) Fine needle aspiration cytology stained with Rius method in quicker diagnosis of medullary thyroid carcinoma. *J Formos Med Assoc*. 106 (9): 728-35.
- [22] Pinto AP, Maia HF, di Loretto C, Krunn P, Tulio S, Collaco LM (2007) Repeating cytological preparations on liquid-based cytology samples: A methodological advantage? *Diagn Cytopathol*. 35 (10): 663-9.
- [23] Herbert A, Johnson J . Personal view (2001) Is it reality or an illusion that liquid-based cytology is better than conventional cervical smears? *Cytopathology*. 12 (6): 383-9.
- [24] Cupisti K, Wolf A, Raffel A, Schott M, Miersch D, Yang Q, Eisenberger CF, Roher HD, Knoefel WT (2007) Long-term clinical and biochemical follow-up in medullary thyroid carcinoma: a single institution's experience over 20 years. *Ann Surg*. 246 (5): 815-21.
- [25] Ball DW (2007) Medullary thyroid cancer: monitoring and therapy. *Endocrinol Metab Clin North Am*. 36 (3): 823-37.
- [26] Moley JF, Fialkowski EA (2007) Evidence-based approach to the management of sporadic medullary thyroid carcinoma. *World J Surg*. 31 (5): 946-56.
- [27] Schlumberger M, Carlomagno F, Baudin E, Bidart JM, Santoro M (2008) New therapeutic approaches to treat medullary thyroid carcinoma. *Nat Clin Pract Endocrinol Metab*. 4 (1): 22-32.

- [28] Dadan J, Wolczynski S, Sawicki B, Chyczewski L, Azzadin A, Dzieciol J, Puchalski Z (2001) Preliminary evaluation of influence of gemcitabine (Gemzar) on proliferation and neuroendocrine activity of human TT cell line: immunocytochemical investigations. *Folia Histochem Cytobiol.* 39 (2):187-8.

IntechOpen

IntechOpen