

Case Report

Metastasis of lung carcinoid in the thyroid gland after 18 years: it is never too late. A case report and review of the literature

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Summary

Metastasis to the thyroid gland is a rare event. To date, only 11 cases of metastasis from neuroendocrine tumors (NETs) originating in the lung have been reported. We present a case of a patient in his 40s harboring two nodules in the thyroid gland that were diagnosed as well-differentiated NET (G1). Eighteen years before the patient underwent a lung lobectomy of the right upper lobe for a bronchial typical carcinoid with metastasis in one lymph node. Normal blood levels of calcitonin virtually ruled out the diagnosis of medullary thyroid carcinoma (MTC) and supported the diagnosis of a possible thyroid metastasis of the previous bronchial NET. Mutational analysis performed on both primary and metastasis tumor tissue did not show any mutation in the 409 genes analyzed.

Key words: neuroendocrine tumor, thyroid metastasis, bronchial carcinoid, metastasis.

Introduction

Neuroendocrine tumors (NETs) develop from neuroendocrine cells throughout the body. They may be non-functioning or hormone-producing, and in lung were classified by WHO 2021 in three categories: typical carcinoid or well-differentiated NETs (G1), atypical carcinoid or moderately-differentiated NETs (G2), and neuroendocrine carcinomas (G3). G1-NETs are the most indolent ones, rarely metastasize and have a better prognosis than the latter.

The most frequent primary neuroendocrine tumor in the thyroid gland is medullary carcinoma (MTC), arising from parafollicular cells (or C-cells), and accounting for 2-3% of all thyroid malignancies. Most MTCs express calcitonin, CEA and TTF1, and may express a large variety of neuroendocrine markers; stromal deposits of amyloid are found in most cases and may be highlighted by Congo red staining. Other rare primary neuroendocrine tumors are intrathyroidal paragangliomas and intrathyroidal parathyroid adenomas.

Metastases to the thyroid from other malignancies have been reported, usually from lung, breast and kidney carcinomas, while metastases from neuroendocrine neoplasia have been found very rarely (1%)¹. We pres-

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ent a case of thyroid localization of a well-differentiated bronchial NET after 18 years from the first diagnosis of malignancy.

Case report

A male patient in his 40s was admitted to our hospital after a few spontaneous tachycardia episodes. Holter ECG was negative and he underwent an ultrasonographic examination of the neck, which found two solid hypoechoic nodules in his thyroid gland, the major in the right lobe (diameter 11 mm) (Fig. 1a), the other in the left lobe (diameter 4 mm), without enlargement of neck lymph nodes. Two consecutive fine-needle aspiration cytology (FNAC) examinations were performed on the larger nodule in two different hospitals, with two different diagnosis: Tir4, suggestive of MTC, in an external laboratory (Fig. 1b), and Tir3B in our structure (Figure 1c). Both FNACs showed thyrocytes with mildly enlarged nuclei, thickened chromatin and eosinophilic cytoplasm (Figs. 1b, 1c). No immunocytochemical staining was performed. Serum levels of calcitonin, carcinoembryonic antigen and thyroglobulin were in the reference range.

Eighteen years before the patient had undergone a right upper lung lobectomy with hilum-mediastinal

lymphadenectomy in an external structure. Histological diagnosis was of central bronchial typical carcinoid (nodule of 42 mm), with metastasis in one of fifteen lymph nodes. Therefore, subsequent adjuvant chemotherapy and radiotherapy were performed. Before thyroidectomy, 18F-FDG PET/CT scan gave negative results, and ^{68}Ga -DOTATOC PET/CT scan showed focal radiotracer uptake in both thyroid lobes, more intense in the right lobe ². After this examination, the patient underwent total thyroidectomy.

Pathology results

At gross examination, the right lobe of the thyroid measured 3.5 x 1 x 1.5 cm, and left lobe measured 2.5 x 2 x 2 cm. At cut section both nodules found at ultrasonography were identified: one of 11 mm in diameter in the right lobe, and the other of 4 mm in diameter in the left lobe, both whitish and firm, apparently well circumscribed.

Microscopically both nodules corresponded to a cellular proliferation with an organoid, trabecular and pseudo glandular growth pattern (Figs. 2a, b) Neoplastic cells were polygonal with eosinophilic cytoplasm and round to oval nuclei characterized by “salt and pepper” chromatin and small nucleoli (Fig. 2c). Necrosis was

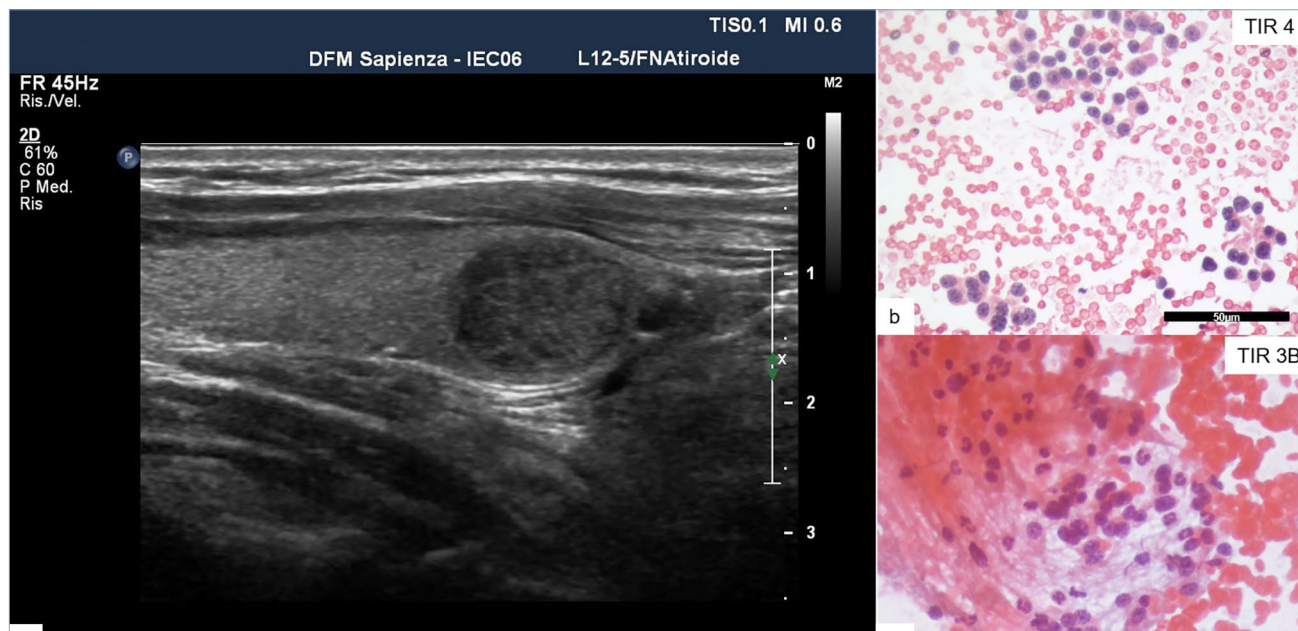


Figure 1. Ultrasonography image of the major nodule of the thyroid which underwent FNA twice (diameter mm 11) (a); cytological aspects of both FNA examinations: the first was classified as Tir4 (b), the second one was classified as Tir3b (c) (classification by Consenso Italiano Citologia Tiroidea SIAPEC-AIT. J. Endocrinol Invest. 2014). Both cytological examinations showed thyrocytes with mildly enlarged nuclei, thickened chromatin and eosinophilic cytoplasm.

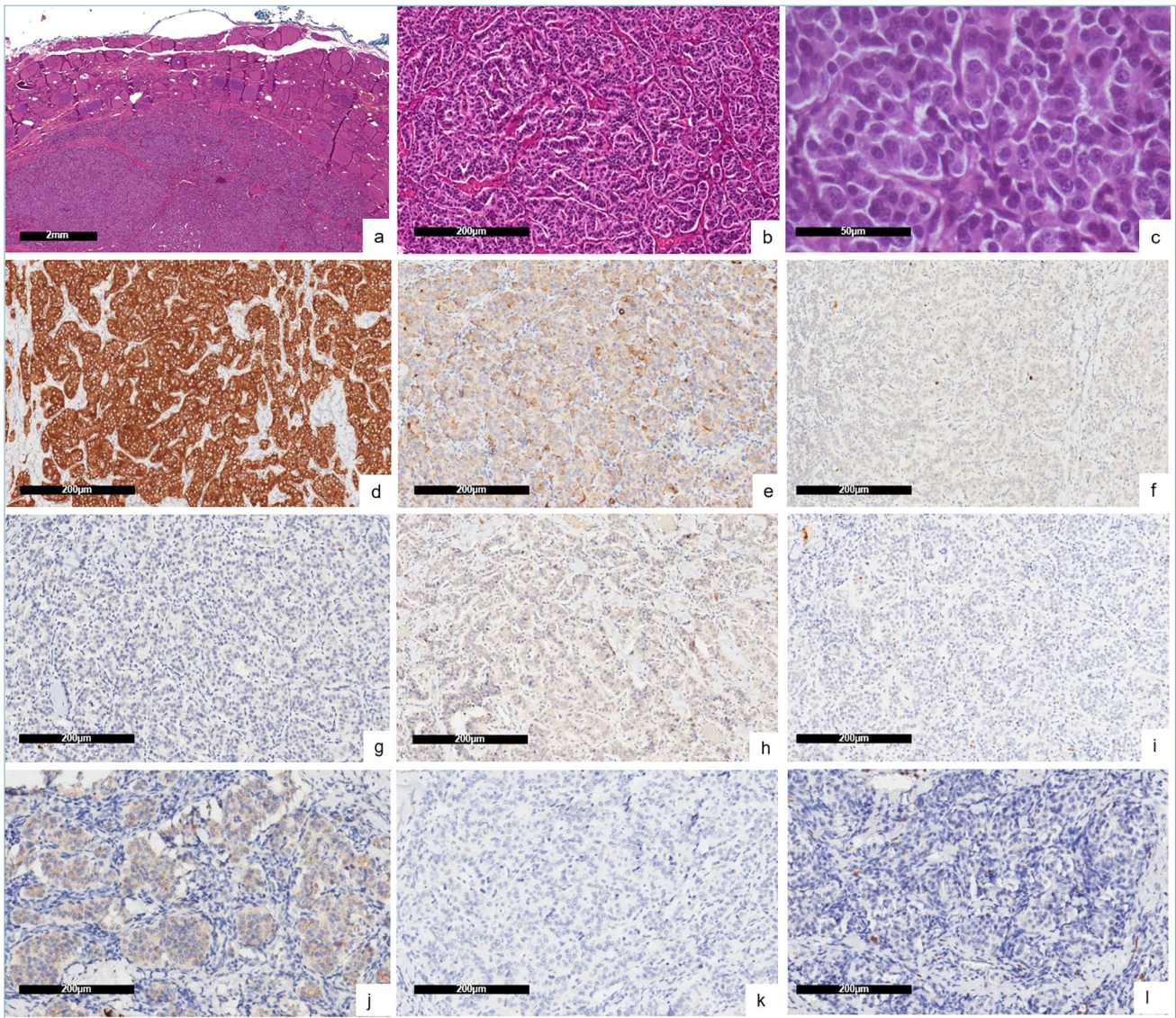


Figure 2. Microscopic images of the larger thyroid nodule in the right lobe (mm 11): thyroid shows a neoplasia (a, 2.5x magnification) with an organoid, trabecular and pseudo glandular growth pattern (b, 20x magnification). Neoplastic cells were polygonal, with eosinophilic cytoplasm and round to oval nuclei characterized by “salt and pepper” chromatin and small nucleoli (c, 40x magnification) (a, b, c: Hematoxylin and eosin stain). Neoplastic cells are positive for Synaptophysin (d), Chromogranin-A (e) and CK AE1/AE3 (dot-like) (j) and show a Ki67 index of 2% (f). Cells are negative for Thyroglobulin (g), Calcitonin (h), CEA (i), CD10 (k) and S100 (l). (d-l: immunostainings, 20x magnification).

absent and mitotic count was low (< 2 mitosis/ 2 mm^2). Both nodules were limited to the thyroid tissue. Neoplastic cells showed immunoreactivity for Synaptophysin (Fig. 2d), Chromogranin-A (Fig. 2e), NSE, CD56 and CK AE1/AE3 (dot-like) (Fig. 2j) while they were completely negative for Thyroglobulin (Fig. 2g), Calcitonin (Fig. 2h), CEA (Fig. 2i), TTF-1, High Molecular Weight Cytokeratin, CD10 (Fig. 2k) and S100 (Fig. 2l). The proliferation rate of tumor cells, evaluated

with Ki-67, was 2% (Fig. 2f). Congo Red staining was negative.

Negative immunohistochemistry for both Calcitonin and CEA associated with normal blood levels of calcitonin virtually ruled out the diagnosis of MTC and supported the diagnosis of a possible thyroid metastasis of the previous bronchial NET of central type according with CD10 immunostaining negativity. Dot-like positive immunostaining for CK AE1/AE3 and S100

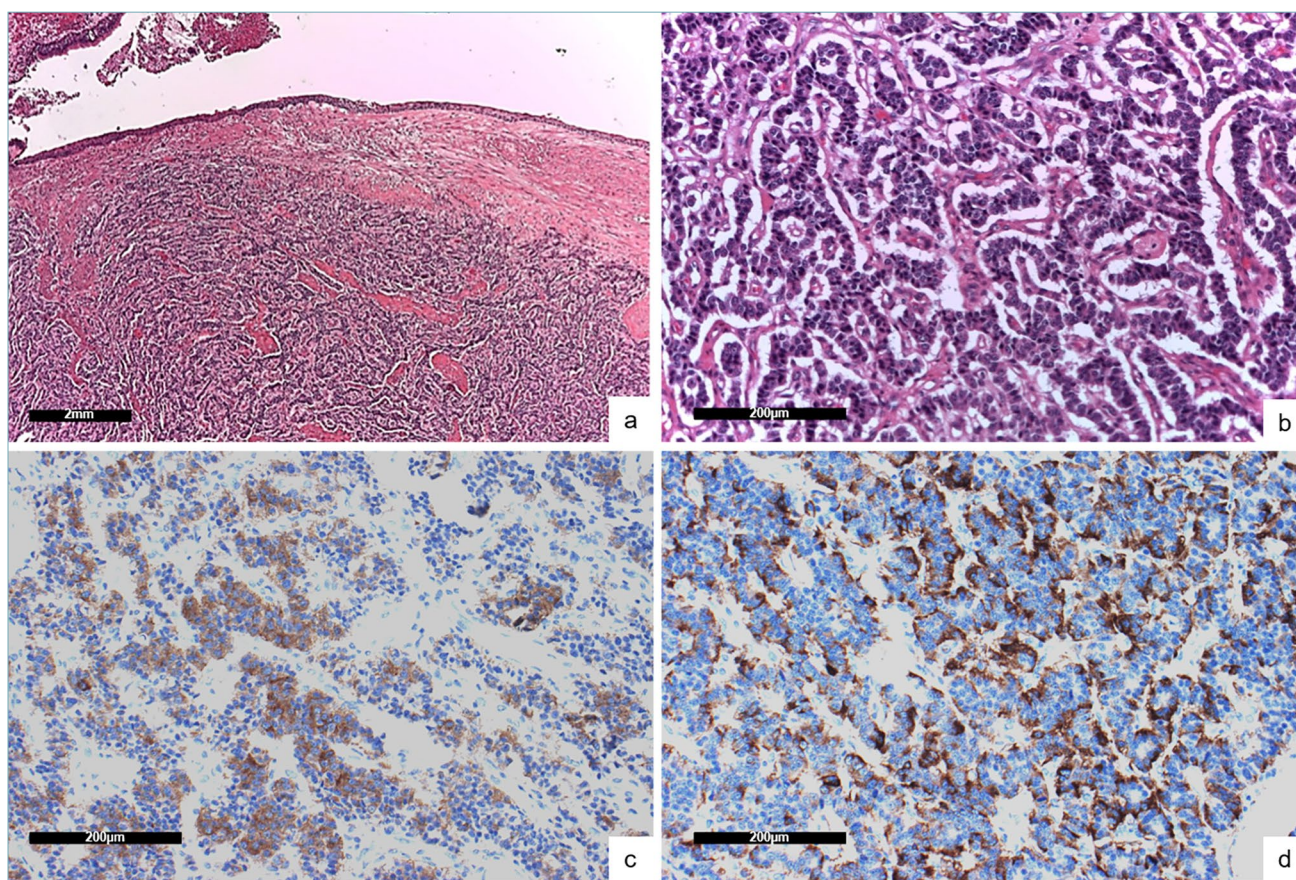


Figure 3. Microscopic pictures of the lung nodule (mm 42): neoplasia (a, 2.5x magnification) with a trabecular and pseudo glandular growth pattern (b, 20x magnification) (a, b: Hematoxylin and eosin stain). Neoplastic cells show positivity for Synaptophysin (c) and Chromogranin-A (d) (c, d: 20x magnification). Ki-67 not shown.

negativity of the neoplastic cells ruled out a possible diagnosis of paraganglioma, a neoplasia rarely described in thyroid gland.

Revision of the previous pulmonary lesion confirmed a bronchial typical carcinoid, with morphological and immunohistochemical features similar to those observed in thyroid (Figs. 3a-d).

Therefore, histological diagnosis of thyroid nodules was multiple metastasis of bronchial typical carcinoid. To date, the patient is alive and clinically followed.

Mutational analysis

Mutational analysis was performed on both lung and thyroid tumors. DNA was obtained from FFPE tumor tissues and from matched non-neoplastic gastric tissue using 10 consecutive 4-µm sections and the QIAamp DNA FFPE Tissue Kit (Qiagen) and qualified as reported elsewhere. The OncoPrint Tumor

Mutational Load (TML) panel with next-generation sequencing assay (ThermoFisher) was used. The assay covers 1.65 Mb including the exons of 409 cancer-related genes.

Sequencing was performed on Ion Torrent platform using 20 ng of DNA for each multiplex PCR amplification and subsequent library construction. The quality of the obtained libraries was evaluated by the Agilent 2100 Bioanalyzer on-chip electrophoresis (Agilent Technologies). Emulsion PCR to clonally amplify the libraries was performed with the Ion OneTouch™ OT2 System (ThermoFisher). Sequencing was run on the Ion Proton (ThermoFisher) loaded with Ion PI Chip v3. Data analysis, including alignment to the hg19 human reference genome and variant calling, was done using Torrent Suite Software v.5.10 (ThermoFisher). Filtered variants were annotated using a custom pipeline based on vcfliib (<https://github.com/ekg/vcfliib>), SnpSift, Variant Effect Predictor (VEP) and NCBI RefSeq database. Additionally, alignments were visually veri-

fied with the Integrative Genomics Viewer (IGV) v2.3 to further confirm the presence of identified mutations. CNV was evaluated using OncoCNV v6.8. BAM files obtained by sequencing of tumor samples were compared to BAM files obtained from blood samples. The software includes a multi-factor normalization and annotation technique enabling the detection of large copy number changes from amplicon sequencing data and permits to visualize the output per chromosome. The two specimens were analyzed for 409 genes included in the TML assay panel. Sequencing achieved an average coverage of 982x in lung carcinoid, 829x in thyroid nodule and 784x in normal sample. No mutation in the 409 genes analyzed was found. The CNV status was estimated for all 409 genes by using sequencing data. Based on the chromosomal position of each gene, the status of chromosome arms was inferred. Lung carcinoid and thyroid nodule shared copy gain for chromosome 5, 7, 9, 10, 14 and 16. Only in the bronchial carcinoid was detected copy gain of whole chromosome 19 and 4p, 6p and 13q arms.

Discussion

Carcinoid tumors of the lung account for < 1% of all lung cancers. Typical carcinoids are usually indolent and have a 5-year survival rate of 90%. Metastases from these tumors are very rare. MTCs are the most frequent primary thyroidal neuroendocrine neoplasms, accounting for 2-3% of all thyroid malignancies. Metastases from different cancer types to the thyroid are very rare; they account for 2% in autopsy series and lung is the most common primary site, while in clinical series renal cell carcinomas are the most frequent metastases found in thyroid gland. Neuroendocrine tumors account for 1% of thyroid gland metastases¹ and in literature only 11 cases are described^{1,3-5}. Our metastasis of bronchial typical carcinoid to the thyroid is the twelfth case reported in literature, and it is the one with the longest time (18 years) between primary lung tumor and thyroid metastasis⁵. It may be very difficult to differentiate MTC from a metastatic nodule of a NET on histological exam because they share morphological features. Immunohistochemistry may be helpful: both MTCs and bronchial carcinoids are usually positive for generic neuroendocrine markers, including chromogranin and synaptophysin. MTCs usually express Calcitonin, TTF1 and CEA, while bronchial carcinoids can rarely express Calcitonin and TTF1. In MTCs negative for Calcitonin, CEA positivity is usually retained. Stromal depots of amyloid are exclusively found in MTCs.

While Ki-67 index is not used as a prognostic factor in MTC, it is very important to distinguish typical from atypical carcinoids. Low Ki-67 index in our case (< 2%) is consistent with the diagnosis of typical carcinoid, and with its indolent clinical course.

Given that, as reported in the literature, lung neuroendocrine tumors show specific molecular alterations, we performed a massive parallel sequencing to corroborate our hypothesis that metastases to the thyroid gland originated from neuroendocrine tumor. In the case presented, negative results of molecular analysis did not give any substantial contribution to demonstrate the pulmonary origin of the thyroid neoplasm. Because of the marked histological similarities, differential diagnosis between MTC and a metastatic nodule from a lung NET is fundamental for the patient's prognosis and therapy. Immunohistochemistry is helpful to distinguish between the two neuroendocrine neoplasms.

The case reported herein further underlines that a neuroendocrine neoplasm in the thyroid is not always a MTC, but clinical, anamnestic, serologic and instrumental data are necessary to guide the pathologist to the right diagnosis.

CONFLICT OF INTEREST

The Authors declare no conflict of interest.

FUNDING

The Authors did not receive support from any organization for the submitted work.

ETHICAL CONSIDERATION

The study complies with ethical standards. The patient gave his informed consent.

AUTHORS' CONTRIBUTION

MDSV contributed to the analysis of the pathologic findings and to manuscript writing; EG collected and critically analyzed clinical data; DB contributed to the analysis of the cytological findings; MB collected and critically analyzed clinical data; RC performed the cytological and histological slides, collected pathological data and contributed to edit the figures of the manuscript; CC contributed to the analysis of the molecular findings; MB contributed to the analysis of the pathologic findings; MS contributed to the mutational analysis; DA contributed to the mutational analysis; AMI collected and critically analyzed clinical data; AS revised the work critically for important intellectual content; CRTdG contributed to the analysis of the pathologic findings and to manuscript writing.

All authors read and approved the final manuscript.

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