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Single lung and bone metastasis 30 years after thyroid cancer onset

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Summary. *Background:* Papillary thyroid carcinoma is the most common thyroid cancer. Lungs and bones are the most frequent sites of metastasis, characterized by a multiple nodular or miliary pattern. A solitary site of papillary thyroid cancer metastasis in lung and bone tissues is quite rare. *Case report:* We describe an unusual case of single bone and single pulmonary metastasis from papillary thyroid carcinoma. These metastases appeared 30 years after the onset of the primary tumour. In parallel, 15 years after the thyroid carcinoma, the patient also had breast cancer, which can typically cause both lung and bone metastases. Therefore there were many doubts about the diagnosis of these two lung and bone lesions: primitive or secondary tumours? and, if secondary, what was their primitive form? thyroid or breast? Immunohistochemical staining of both lung and bone lesions for different tumour markers was performed in order to determine the cancer histogenesis. *Conclusions:* In order to perform a differential diagnosis of metastasis and to choose an effective therapy, the oncologist must consider various parameters, such as thorough medical history evaluation and careful immunohistochemical analysis. A long-term relapse from papillary thyroid cancer should also be borne in mind.

Key words: papillary thyroid cancer, bone metastasis, lung metastasis, breast cancer, follow up

«Singola metastasi polmonare ed ossea a 30 anni dall'insorgenza di un tumore tiroideo»

Riassunto. *Background:* Il carcinoma papillare della tiroide è il tumore tiroideo più comune. Il polmone e l'osso sono le sedi di metastasi più frequenti, caratterizzate da una struttura miliare o multi-nodulare. Una singola sede di metastasi polmonare e ossea da carcinoma papillare tiroideo è molto rara. *Caso clinico:* Noi descriviamo un raro caso di singola metastasi polmonare ed ossea da carcinoma papillare tiroideo comparsa 30 anni dopo l'insorgenza del tumore primitivo. In parallelo, 15 anni dopo il tumore tiroideo, alla paziente è stato diagnosticato un carcinoma mammario, che tipicamente può dare sia metastasi ossee che polmonari. Pertanto si presentavano alcuni dubbi diagnostici riguardo la natura di queste lesioni: primarie o secondarie, e, se secondarie, quale primitività, tiroide o mammella? È stata allora effettuata un'indagine immunoistochimica su entrambe le lesioni, polmonare ed ossea, con differenti marcatori tumorali per determinarne l'istogenesi. *Conclusioni:* Per arrivare ad una diagnosi differenziale e scegliere una terapia efficace, l'oncologo deve tenere in considerazione diversi parametri, tra cui una attenta valutazione della storia naturale della malattia insieme ad una specifica analisi immunoistochimica. Inoltre è fondamentale considerare anche la possibilità di metastasi a distanza da carcinoma papillare tiroideo, nonostante un lungo intervallo libero da malattia.

Parole chiave: carcinoma papillare tiroideo, metastasi ossea, metastasi polmonare, carcinoma mammario, follow up

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer, representing approximately 80% to 90% of all newly diagnosed thyroid cancers (1). PTC is typically characterized by an indolent clinical course, in comparison to other thyroid malignancies. Radiation is the most important risk factor for PTC. PTC commonly metastasizes to the lymph nodes (1), and distant metastases may occasionally occur at the time of presentation and account for 9% to 10% during the follow up (2). Metastases can be located in the lungs, bones, lungs and bones together, or in other sites such as the skin, liver and brain (3).

Thyroid cancer pulmonary and bone metastases usually show a multiple nodular pattern or a miliary pattern throughout both lungs and in various different bone segments. Single bone or pulmonary metastases are quite rare and there are only limited reports. We describe an unusual case of single bone and single pulmonary metastasis from thyroid cancer 30 years after its onset.

Case report

A 65 year-old woman, a non-smoker treated with ACE inhibitors for hypertension, was referred to our Institute for evaluation of a single nodule in the left lung and a single bone lesion on the tenth thoracic vertebra.

The patient was completely asymptomatic. Her performance status (PS) was 0 on the ECOG scale. In her past medical history, 30 years earlier, she had undergone lumpectomy in the left thyroid lobe for a thyroid cancer, the histological evaluation of which was not available. Subsequently, in 1995, she underwent left mastectomy with axillary lymphadenectomy for a well-differentiated ductal infiltrating carcinoma, 21 mm diameter, with 1 among 21 nodes presenting metastatic repetition, oestrogen receptor expression 15%, progesterone receptor 22%, Ki 67 8%. HER2 status was not evaluated; the tumour classification was pT2, pN1, pMO. She was treated with adjuvant hormone therapy, Tamoxifen 20 mg daily.

In 2007, a routine radiography of the chest showed a left lung opacity, so a CT scan was done and showed a well-defined, lobulated, nonnhomogeneous nodule, without calcification inside, measuring 22 mm, located on the left lower lobe, in the paracardiac area (Fig. 1a) and an osteolytic area in dorsal vertebra D10 extending caudally into the left paramedian site (Fig. 1 b-c).

Routine laboratory tests were all normal, including serum tumour markers, such as CEA and Ca 15.3; thyroid-stimulating hormone (TSH) and thyroglobulin had not been evaluated at the time of admission.

An (18) F-fluorodeoxyglucose positron emission tomographic image showed an increase in the accumulation of the metabolite with a maximum standardized uptake value (S.U.V.) of 6.8 in the pulmonary lesion and an S.U.V. of 17.9 in the osteolytic area in dorsal

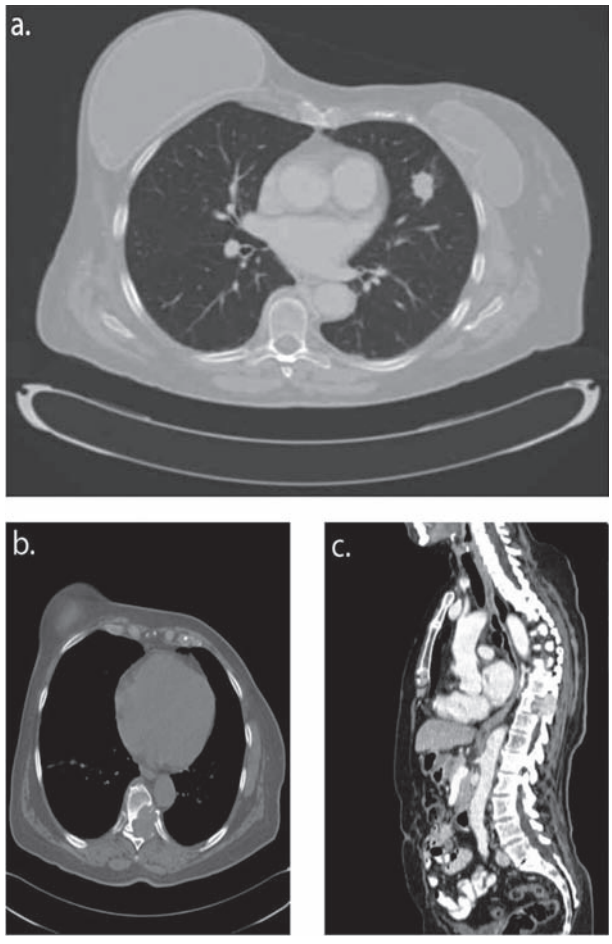

Figure 1. Computed tomographic scan of the chest showing **a)** a lobulated, nonhomogeneous nodule, measuring 22 mm, located on the left lower lobe, **b-c)** an osteolytic area in dorsal vertebra D10 in axial **(b)** and sagittal (**c**) view.

vertebra D10 extending caudally into the left paramedian site.

Due to uncertainty whether the lesions were primitive or secondary (breast or thyroid), a CT-guided biopsy of the lung lesion was performed to obtain a final histological diagnosis.

A first histological evaluation described a well-differentiated bronchoalveolar carcinoma, though of doubtful origin. Thus, the possibility of a third primitive site was suggested: a primary lung cancer with a single bone metastasis in a patient who in her medical history had had two previous tumours (breast and thyroid).

We then performed a new histological examination and an immunohistochemical evaluation of the previous lung biopsy. Haematoxylin and eosin staining revealed a well differentiated papillary adenocarcinoma with psammona bodies, grooves and nuclear pseudo-inclusions (Fig. 2a). Immunohistochemistry demonstrated that cancer cells were negative for oestrogen and progesterone receptor and for cytokeratin 20 (CK20), while they were positive for cytokeratin 7 (CK7) (Fig. 2b), for thyroglobulin and for Thyroid Transcription Factor 1 (TTF1) (Fig. 2c).

A diagnostic whole-body radioiodine scan was done and showed foci of intense uptake on the middle region of the neck, in the right laterocervical region, in the lower left lung field and on the tenth thoracic vertebra.

Taken all together, these findings were consistent with a diagnosis of lung and bone metastasis from the papillary thyroid cancer of 30 years earlier.

Surgical treatment of the residual thyroid gland was done to shoot down residual tumour tissue and to enhance the effect of radioiodine treatment in the management of visceral metastasis. A thyroidectomy with laterocervical lymphadenectomy was performed and the histological evaluation revealed a well-differentiated papillary adenocarcinoma exceeding the capsule, 3 out of 7 of the examined nodes had metastatic repetition, tumour classification pT3, pN1, pM1.

The patient then underwent metabolic treatment with radioiodine I-131 (cumulative activity 7400 MBq). This treatment caused almost complete thyroid residue ablation and eradication of the metastatic pulmonary site but not of the metastatic bone site.

Considering the insensitivity of the bone metastasis to radioactive iodine, stabilization with screws on the eighth, ninth, eleventh, twelfth thoracic vertebrae and titanium mesh placement on the left hemisoma of the tenth thoracic vertebra was performed and tumour tissue was excised. The histological examination revealed a well-differentiated metastatic papillary adenocarcinoma similar to the primitive thyroid tumour.

Post-therapeutic scans were performed and the thyroglobulin serum (Tg) level was tested. To date, follow-up whole-body radioiodine scans have remained negative and the Tg values have not changed.

Discussion

We present an unusual case of solitary bone and pulmonary metastases 30 years after a primary thyroid cancer. The most common sites of thyroid metastases are the lungs (50%), followed by bones (25%) and lungs and bones together (20%), the first having a better prognosis than the second. Other metastatic areas are less common (5%) and involve mediastinum, brain, liver and skin. The reported 10-year survival rates after discovery of distant metastases range from 24% to 42%, but multi-site disease is associated with a higher rate of mortality which can be as much as 92% at 5 years (3, 4). Pulmonary and bone metastases from thyroid cancer usually appear with a multiple nodular pattern or a miliary pattern throughout both lungs and in different bone segments. A single pattern of pulmonary and bone metastasis from thyroid cancer is quite rare. Above all, though other cases of single-pattern pulmonary metastasis after thyroid cancer have been published in the literature, in our patient the lung metastasis was concomitant with a single bone lesion which appeared after a very long relapse-free period of survival, 30 years after surgery for primary thyroid cancer. Distant metastases from differentiated thyroid cancer have also been reported many years after diagnosis, but usually within 20 years. The case here described suggests that a long-term follow up is important for patients with differentiated thyroid cancer.

Some authors have reported occult thyroid cancer cases diagnosed only after metastasectomy (5). Others have reported cases describing single pulmonary

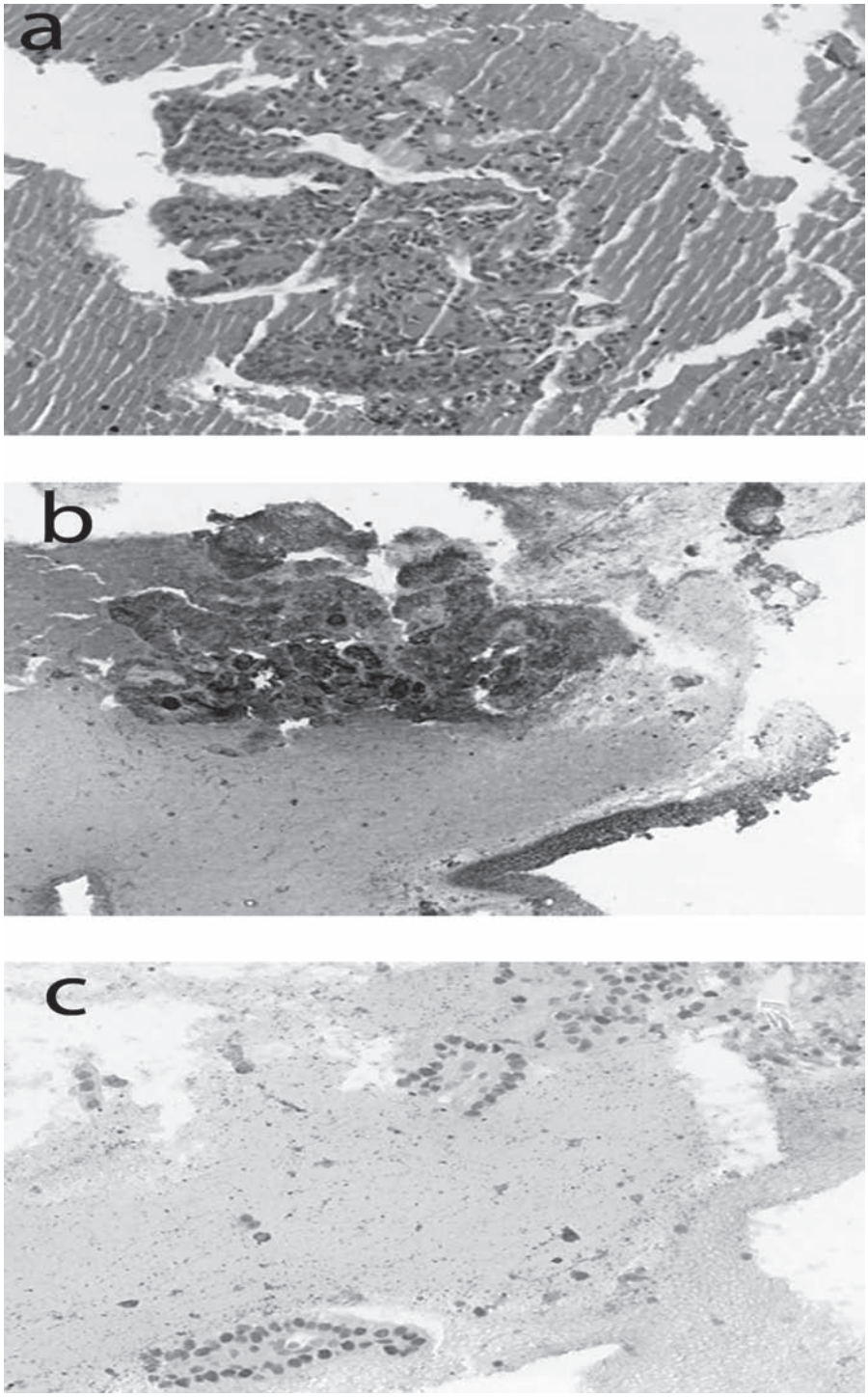

Figure 2. Haematoxylin and eosin staining of a well-differentiated papillary adenocarcinoma showing psammona bodies, grooves and nuclear pseudo-inclusions (**a**). Adenocarcinoma immunoperoxidase staining positive for cytokeratin 20 (CK20) (**b**) and for Thyroid Transcription Factor 1 (TTF1) (**c**).

metastasis after a previous primary tumour, as in our case (6). Tubiana and colleagues reported that 24% of recurrent thyroid cancers, including pulmonary metastases, occurred as much as 20 years after the initial treatment in patients with differentiated thyroid cancer (7). Our case has the longest reported interval between the initial primary thyroid cancer and relapse of disease. This case has the peculiarity that the sin-

gle metastatic pulmonary lesion is concomitant with a single bone lesion. The history of our case indicates that in order to reach a correct diagnosis of single pulmonary nodule with a simultaneous single bone lesion, the patient's previous history of extra-pulmonary malignancy should be taken into consideration. The various possibilities of lung and bone lesions in our patient included: benign lesions (such as granulomas), a primary lung cancer with a single bone metastasis, metastatic pulmonary and bone sites from one of the two previous primary tumours. Furthermore, it was of extreme importance to differentiate between primitive thyroid and primitive breast cancer. So, once a benign tumour had been excluded, we were forced to make a careful evaluation of the clinical history of the primary cancers, their features and treatment. Careful study of a medical history means the pathologist uses several tumour markers and of cytokeratin (CKs) in immunohistochemical analyses; these can support a differential diagnosis of cancer. Cytokeratin 7 and 20 are the most commonly used CKs and expression of these could be useful to detect the origin of the cancer by differential diagnosis of the pulmonary lesions. Both lung adenocarcinomas and thyroid tumours usually express CK7 but not CK 20; thyroglobulin positivity, which is produced by thyroid tissues exclusively, is also a valuable marker to distinguish thyroid cancers from other tumours. Hence, the combination of these markers helps determine the differential diagnosis for a malignant lesion from an unknown primary cancer. When single lung and bone nodules are encountered in patients with a history of previous thyroid cancer, careful evaluation of their medical history is necessary and the possibility of delayed metastases must be kept in mind, even if a long time has gone by, and a careful long-term follow-up is mandatory for differentiated thyroid cancers.

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