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Myoma Hot Spot: Tumor-to-Tumor Metastasis of Thyroid Origin into Uterine Leiomyoma

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Established Facts

- Distant tumor spread from differentiated thyroid cancer is rare.
- The most common metastatic sites include bone and lung.
- Metastases to brain, eye, breast, liver, kidney, muscle, and skin are infrequent.
- These metastases almost always appear in advanced-stage disease.

Novel Insights

- Differentiated thyroid cancer may very rarely spread to the visceral pelvis (uterus, ovary).
- Tumor-to-tumor intramyoma uterine metastasis of papillary thyroid carcinoma origin is reported as a very rare dedifferentiated (trabecular) tumor spread of intermediate prognosis.
- Metastasis was shown as a "hot spot" hypervascular nodule.

Keywords
Papillary thyroid cancer · Metastasis · Myoma · Tumor spread · Rising thyroglobulin

Abstract
Introduction: Distant metastases of papillary thyroid cancers are rare. Most common metastatic sites include bone and lung, whereas metastases to brain, eye, breast, liver, kidney, muscle, and skin are infrequent and almost always appear in advanced-stage tumor disease. Metastases to ovary and/or uterus are even scarcer. We report herein a very exceptional case of asymptomatic malignant-to-benign tumor-to-tumor metastasis of thyroid origin into a uterine leiomyoma. ***Case Presentation:*** We present the case of a 53-year-old female patient who had a previous history of pT1b N0 M0 R0 papillary carcinoma of the lower left thyroid lobe, treated by total thyroidectomy and central lymph node dissection

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and two successive administrations of radioactive treatment with iodine-131. Six years later, follow-up imaging disclosed an asymptomatic slow-growing 40-mm-long pedicled subserous heterogeneous uterine myoma including a 12-mm hypervascular nodule, which was suspicious for thyroid malignancy on MRI. ***Discussion:*** Histopathology of a hysterectomy specimen disclosed a hypervascular well-limited poorly differentiated trabecular carcinomatous infiltration within the uterine leiomyoma. The immunohistochemical profile of the suspicious nodule was compatible with a thyroid origin. ***Conclusion:*** A hypervascular "hot spot" intramyoma nodule was the diagnostic clue in a clinical context of hematogenous tumor spread of thyroid origin (increased thyroglobulin level).

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Introduction

We would like to highlight an exceptional case of tumor-to-tumor metastasis from a well-differentiated papillary thyroid carcinoma (PTC) into a benign uterine leiomyoma.

Case Presentation

We present the case of a 53-year-old female patient with a slow-growing latero-uterine mass on serial control CT examinations. She had no prior radiotherapy nor a familial thyroid disease context. The patient reported a previous history of well-differentiated pT1b N0 M0 R0 papillary carcinoma of lower left thyroid lobe, treated by total thyroidectomy and central lymph node dissection in March 2012. The size of the papillary thyroid tumor was 12 mm. PTC was of pure common papillary histological pattern (Fig. 1). Neither thyroid capsule invasion nor extrathyroid extension had been found on a histopathology specimen. No lymph node metastases were found. In June 2012, patient was administered radioactive treatment with iodine-131. Whole-body scintigram did not show any uptake foci; as serum thyroglobulin (Tg) level was still detectable (Tg = 10,5 ng/mL, anti-Tg antibodies negative), administration of a second radioactive treatment with iodine-131 was performed in April 2013 [1]. Between April 2013 and October 2018, the patient had the usual oncological follow-up (including physical examination, thyroidian biological assays, and TEP scan). Increasing serum Tg level in 2013 was concomitant with the occurrence of lung metastases without any mediastinal or bone metastasis. In October 2018, imaging disclosed a 40-mm-long pedicled subserous heterogeneous uterine myoma presenting with edematous remodeling and a suspect 12-mm vascularized "hot spot" nodule (Fig. 2a–c).

Given the MRI feature of this growing uterine myoma and the rising serum Tg level curve (220 ng/mL), the patient underwent further interadnexal hysterectomy. Histopathological examination found a largely hyalinized leiomyoma presenting at its center a poorly differentiated trabecular carcinomatous infiltration (Fig. 2d) whose immunohistochemical profile was compatible with a thyroid origin, staining positive for $CK7^+$, $CK20^-$, $TTF1^+$, and Tg^+ (Fig. 3). A second look of the initial papillary cancer and of the uterine metastasis was performed by another specialized pathologist, confirming these results. When uterine metastasis was discovered, the patient also had diffuse visceral metastatic spread including pulmonary and bone metastases.

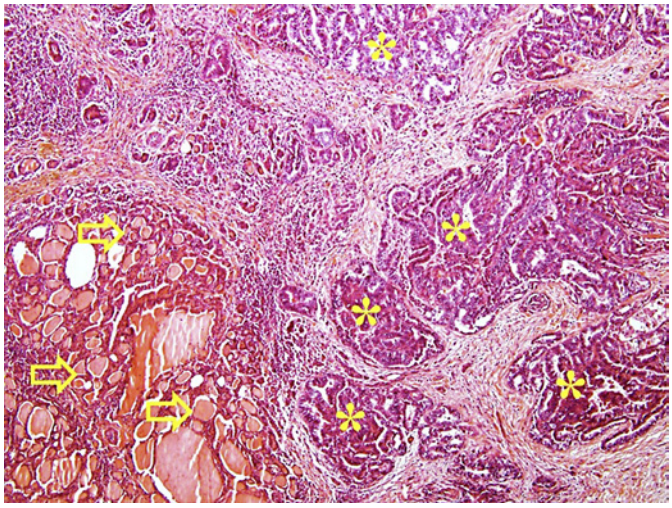

Fig. 1. Histopathology of the primary papillary thyroid cancer. Histopathological specimen of the primary differentiated T1b thyroid tumor (hematoxylin and eosin, ×10). Histological features of classical common papillary carcinoma are shown: papillary architecture within the malignant follicles (asterisks: malignant papillae) is to be compared to that of normal follicles (arrows). Typical associated nuclear features like ground glass appearance, nuclear crowding, and nuclear grooving were displayed on hematoxylin and eosin (×40, not shown). Mitotic figures were sparse. There were no arguments in favor of solid, tall-cell, and columnar/trabecular variants.

Discussion

To our knowledge, this is the first case of malignant-to-benign tumor-to-tumor metastasis of well-differentiated PTC into a benign uterine myoma reported in the literature so far. PTC is the most common well-differentiated malignancy (65–80% of thyroid tumors) and generally has a good prognosis [1]. PTC is indolent and the 10-year survival rate is >90%. Although the prognosis is excellent, certain histopathological features portend a higher risk of tumor recurrence and cancer-related mortality, including age >45 years, male sex, carcinoma size >2 cm^3, invasion into surrounding tissue, histological subtype, and distant metastasis. It spreads mostly by lymphatic channels and metastasis to lymph nodes is frequent; however, this does not affect prognosis.

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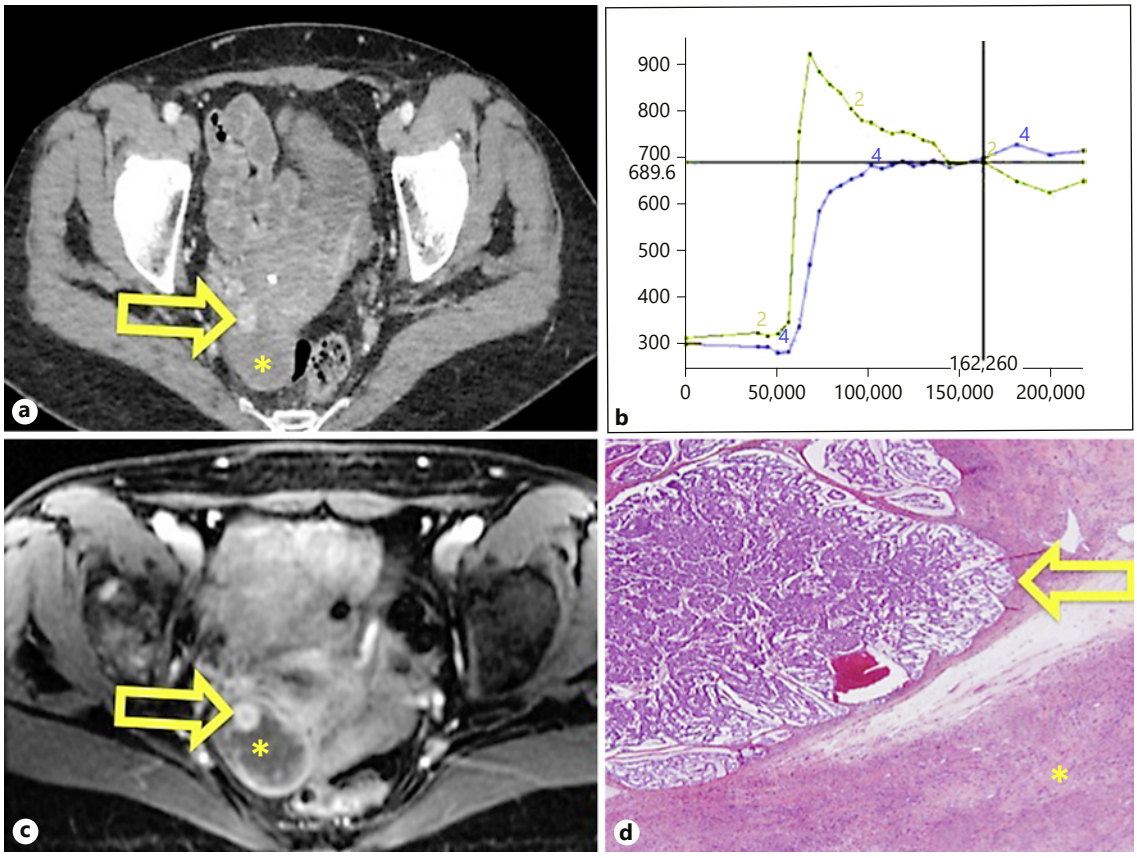

Fig. 2. Imaging features on CT, MRI, and hematoxylin and eosin of "hot spot" intramyoma nodule. **a–c** CT (**a**) and MR (**c**) pelvic axial images showing a "hot spot" 12-mm nodule (arrow) within 40 mm of the growing uterine myoma (asterisk) and increased serum Tg level. Contrast-enhanced MR perfusion sequence (**b**) shows the early enhancement peak and descending plateau (arterial phase, yellow curve) of the 12-mm trabecular metastasis compared to delayed enhancement of the rest of the uterine myoma (blue curve). **d** Histology of the uterine "hot spot" nodule (arrow) showing trabeculae and nests of tumor cells separated by hyalinized stroma (hematoxylin and eosin; hematoxylin and eosin, ×4). Note the capsule separating the metastasis from the surrounding myoma (asterisk).

The histological subtypes of PTC associated with worse prognosis are tall-cell, insular, hobnail variants. The histological trabecular pattern is considered a poor dedifferentiation from the primary origin and of poor prognosis [2, 3].

Lymphatic metastases usually involve the neck and upper mediastinal lymph nodes, very rarely the axillary or retropharyngeal lymph nodes. Distant metastases of PTC are rare and have a substantial impact on prognosis. The most common sites include lung (72–76%), mediastinum (24%), and bones (19–23%), while brain, scalp, eye, nasal cavity, salivary glands, breast, liver, kidney, and muscle are rare sites of metastases [4].

The role of angiogenesis and lymphangiogenesis in thyroid cancer pathogenesis has not been elucidated; the patterns for tumor behavior and metastatic spread vary according to tumor type, and whether differences in the angiogenic or lymphangiogenic phenotype influence the route for tumor metastases or determine a more aggressive behavior has not been fully explored.

Some authors have demonstrated that angiogenesis is reduced in thyroid proliferative lesions compared with nonthyroid tissue. However, VEGF-A expression is upregulated in thyroid cancers. Lymphangiogenesis and VEGF-C expression are increased in thyroid tumors prone to lymphatic metastases. This may explain the differences in metastatic behavior between papillary and follicular thyroid cancer [5].

In addition to its strong correlation with PTC, the *BRAF* V600E mutation has also been associated with a poorer prognosis and a higher recurrence rate. The *BRAF* V600E mutation was not investigated at our institution

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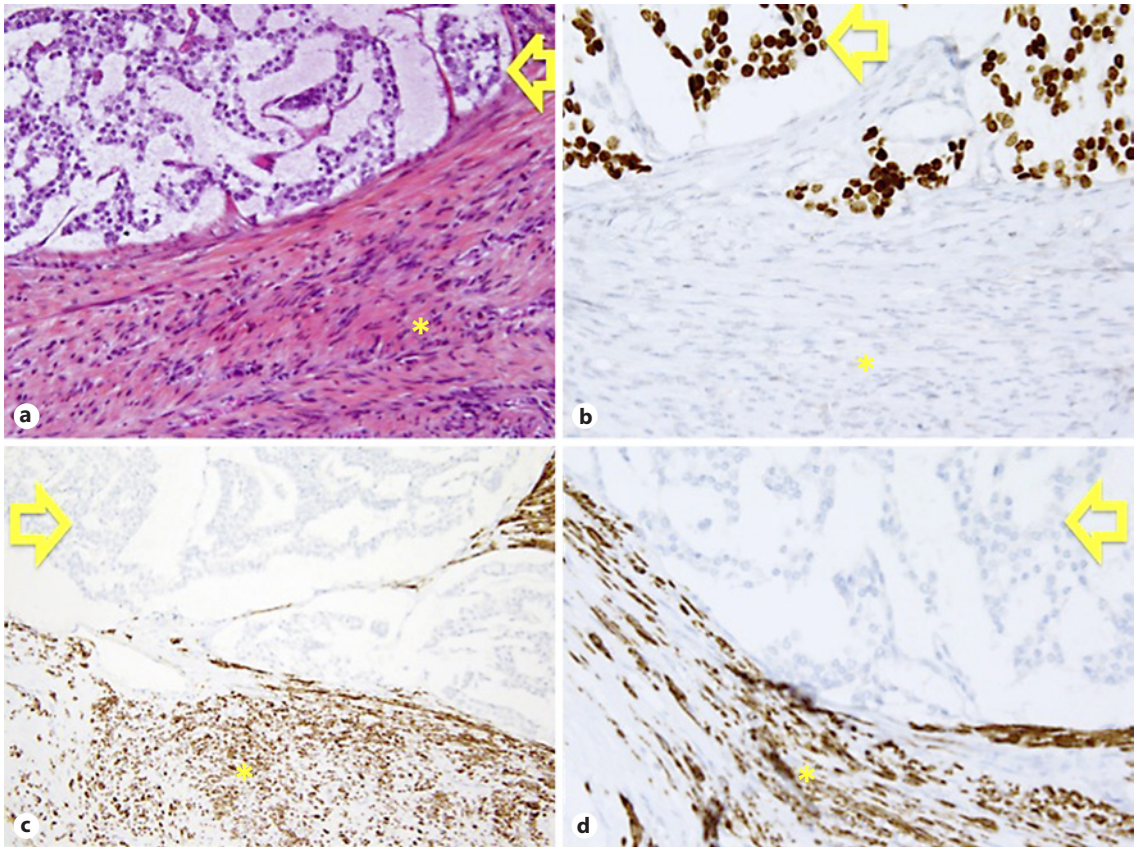

Fig. 3. Histopathology diagnosis by immunostaining. **a** Histology of the uterine "hot spot" metastatic nodule (arrow) and the surrounding benign myoma (asterisk) separated by hyalinized stroma (hematoxylin and eosin, ×20). There is no tumor necrosis as in undifferentiated carcinoma. True papillary formations with fibrovascular cores are absent, thus differentiating from the classical type. The trabecular variant has a less favorable prognosis than classical PTC, but higher survival than poorly differentiated carcinoma. **b** Nuclear marking of the malignant contingency by TTF1 antibody staining (×40, arrow); to be compared to surrounding myoma (asterisk). The tumor can be distinguished from medullary thyroid carcinoma by Congo red negativity, positive Tg immunoreactivity, and negative calcitonin immunoreactivity. **c**, **d** Immunostaining positive for desmin (**c** ×20, **d** ×40) in the myoma (asterisk) surrounding the trabecular metastasis (arrow).

on paraffin-embedded tissues on the primary cancer and uterine metastasis, for the following reason: BRAF antibody was not available at histopathology laboratory at that time, and the original specimen available was not sufficient to perform molecular biology test.

Metastases to ovary and/or uterus are very scarce [6–8]. Those metastases almost always appear in advanced-stage tumor disease. Reported primary tumors metastasizing to the uterus include breast (43%), colon (17.5%), stomach (11%), pancreas (11%), gallbladder (5%), lung (5%), cutaneous melanoma (3%), urinary bladder (3%), and at last thyroid (2%) [7]. Uterine metastasis of medullary/papillary thyroid origin has been reported without ovarian involvement [6, 7]. Razia et al. [9] reported an exceptional case of disseminated tumor spread from breast cancer to endometrial polyp, cervix, and leiomyoma [9].

In the present case, widespread tumor occurred 6 years after thyroidectomy and iodine-131 therapy. There was hematogenous tumor spread to the patient's lung and bone. Interestingly, the sole pelvic metastasis was a uterine metastasis, which was disclosed inside the myoma as a "hot spot" hypervascular nodule on CT and MRI. Noteworthy, the hot spot nodule (uterine metastasis of thyroid origin) showed poor prognosis trabecular differentiation, whereas the primary thyroid tumor displayed a classical well-differentiated histological feature (Fig. 3).

Microfollicular/trabecular carcinoma has intermediate behavior compared to undifferentiated carcinoma. This histological subtype of PTC is characterized by a

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predominantly (>70%) solid growth pattern, retention of cytologic features typical of papillary carcinoma (nuclear elongation, chromatin clearing, nuclear grooves, and pseudoinclusions), and absence of tumor necrosis (Fig. 2d, 3) [4, 10].

Considering differential diagnoses, we hypothesize either for an initially missed microtrabecular thyroid carcinoma on histopathological findings of primary, or for a double component of the distant tumor spread. Finally, we can rule out a trabecular primary carcinoma that might have developed on an exceptional ectopic uterine thyroid tissue [11].

As the patient's serum Tg level had increased over time after thyroidectomy and as the uterine mass had grown concomitantly with lung and bone metastases, the diagnosis of hematogenous metastatic disease of PTC origin into the uterus in a clinical context of widespread disease was retained as the final diagnosis.

In conclusion, this is the first report of tumor-to-tumor intramyoma uterine dedifferentiated metastasis of a monocentric well-differentiated PTC primary, presenting as an MRI "hot spot" growing pelvic mass in a context of hematogenous spread (bone, lung) and rising Tg 6 years after treatment. The histopathological trabecular pattern may explain the aggressive tumor behavior.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects gave their written informed consent to publication of their case and images.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Substantial contributions to the conception and design of the work: Dr. Bertrand, Dr. Iannessi. Substantial contributions to the acquisition, analysis, and interpretation of data for the work: Dr. Peyrottes, Prof. Thyss, Dr. Lacout, and Dr. Marcy. Drafting the work and revising it critically for important intellectual content: Dr. Marcy. Final approval of the version to be published: all authors.

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