



# Papillary thyroid cancer with suspicious uterine cervix metastasis: a case report and literature review

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**Background:** Distant metastasis (DM) of papillary thyroid cancer (PTC) is rare but significantly associated with decreased survival. Accurate clinical staging at initial diagnosis and during follow-up is essential.

**Case Description:** We report the case of a 38-year-old woman diagnosed with PTC in the left isthmus who presented with a suspicious uterine cervix metastasis during follow-up after total thyroidectomy. She had neither medical history nor family history of thyroid cancer. During surgery, extensive central node metastases were found, and bilateral total thyroidectomy was performed. Even after three rounds of radioactive iodine (RAI) ablation, persistently elevated serum thyroglobulin (Tg) levels, combined with a suspicious finding on the whole-body scan (WBS) and fluorodeoxyglucose positron emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT), led to the clinical suspicion of uterine cervix metastasis from PTC. Hysterectomy confirmed the pathology of chronic cervicitis. No hidden malignancy was observed. After surgery, negative imaging findings and decreased serum Tg levels were observed.

**Conclusions:** This case contributes to the discussion of differential diagnostic problems in the setting of clinical and pathological investigations of PTC. However, based on the relevant rationales, through multidisciplinary discussion, this patient can ultimately obtain a better prognosis. Understanding the pitfalls of imaging modalities and continuous efforts to overcome the limitations of the diagnostic process are crucial for future treatment.

**Keywords:** Papillary thyroid cancer (PTC); distant metastasis (DM); uterine cervix; case report

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## Introduction

Papillary thyroid cancer (PTC) is the most common type of thyroid malignancy and accounts for the recent major increase in the incidence observed worldwide (1,2). Locoregional lymphatic spread is frequent in PTC and is reported in approximately 30–90% of cases (3). However, PTC is well-known for its relatively indolent disease course and favorable prognosis, with a 5-year survival rate of more than 95% and a 10-year survival rate of up to 90% (4).

Distant metastasis (DM) of PTC is rare, with a 1–9%

incidence at the initial diagnosis or during follow-up (5,6), and the most common site of DM is the lung followed by the bone, and rare metastases are found in the brain, breast, kidney, liver, and skin (7). DM of PTC is associated with substantial decrease in the survival rate, with a reported 10-year disease-specific survival rate of 50–75% (8).

An aggressive treatment strategy is required in the management of PTC with DM. However, rare metastatic sites of PTC are neither easily predicted nor detected in the clinical setting, leading to their oversight during treatment. Accurate clinical staging at initial diagnosis and during

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follow-up is essential.

In this report, we present a rare case in which a suspicious uterine cervix metastasis was detected in a patient with PTC during follow-up after total thyroidectomy. Empirical evidence of persistently elevated serum thyroglobulin (Tg) levels and a suspicious finding in the whole-body scan (WBS) led to the clinical suspicion of uterine cervix metastasis from PTC. Surgical resection in the form of total hysterectomy confirmed the pathology of chronic cervicitis and the absence of malignancy. However, decreased serum Tg levels with negative image findings after surgery provided insight into the patient's current disease status and guidance to future treatment strategy. We present the following case in accordance with the CARE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-22-210/rc>).

## Case presentation

### Patient

A 38-year-old woman was referred to our hospital for an incidentally discovered thyroid nodule located in the isthmus, which was diagnosed as PTC by fine needle aspiration biopsy (Bethesda category VI). She had no noticeable symptoms and no past medical history except for surgical excision of breast fibroadenoma. She had neither thyroid disease nor irradiation exposure and had no family history of thyroid cancer.

Physical examination of the neck revealed a hard, ill-defined, movable nodule in the left isthmus measuring approximately 0.6 cm in diameter. There was no cervical lymphadenopathy. Laboratory serum tests including complete blood count, electrolytes, and thyroid function were normal. Ultrasound (US) of the neck showed a solid, hypoechoic, irregular nodule with microcalcification in the left lower isthmus. The lesion measured 0.64 cm in diameter at the longest point on the longitudinal view, and anterior capsular invasion (r/o T3a stage) was suspected. An enlarged extrathyroidal nodule with a round shape, 0.6 cm in maximum diameter, was identified in the left lower posterior portion, suspicious of a reactive lymph node (LN) or parathyroid lesion.

A cervical magnetic resonance imaging (MRI) scan with gadolinium contrast revealed that an approximately 0.5 cm enhancing mass at the left isthmus was seen with clear lining of the trachea, and the sternothyroid muscles seemed intact. No abnormal LN enhancement was found. None of

the MRI findings suggested pulmonary or bone metastases.

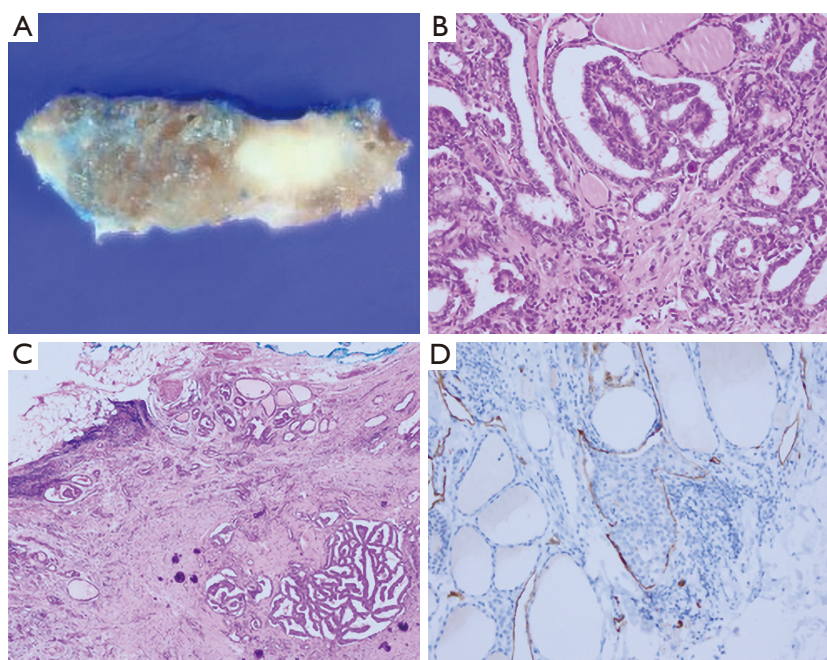
### Thyroid surgery

Left hemithyroidectomy with isthmusectomy under general anesthesia was recommended for the patient. A hard, irregular nodule was detected with intact thyroid capsules. After thyroidectomy, elective ipsilateral central compartment neck dissection (CCND) was conducted. The procedure included level 6 prelaryngeal, pretracheal, and paratracheal LNs. During pretracheal LN dissection, three enlarged, dark-colored LNs were detected and resected. Harvested LNs were sent for frozen analysis and were reported as three metastatic LNs with a maximum diameter of 0.6 cm. When we performed left paratracheal LN dissection, an enlarged LN was discovered, and frozen analyses revealed one 0.6 cm metastatic LN. As all resected LNs were identified as metastases, we proceeded to perform completion thyroidectomy. The patient was informed of the multiple clinically apparent central LN metastases and subsequent completion thyroidectomy. The patient was administered 100 µg of levothyroxine from postoperative day 1 and had an uneventful postoperative recovery without any complications.

### Pathology

Gross examination of the total thyroidectomy with CCND specimen showed an ill-defined whitish infiltrative mass in the isthmus, measuring 0.7 cm × 0.5 cm × 0.3 cm (*Figure 1A*). In hematoxylin and eosin (H&E)-stained slides, papillary microcarcinoma with a classic papillary structure was identified (*Figure 1B*). There was focal microscopic extrathyroidal extension without resection margin involvement (*Figure 1C*). Multiple psammoma bodies were scattered in the background thyroid parenchymal tissue combined with chronic lymphocytic thyroiditis. Immunohistochemical staining of D2-40 (podoplanin) identified lymphatic vessel invasion around the tumor (*Figure 1D*), which was not clearly observed in the H&E slides. Blood vessel invasion was absent. Molecular studies showed the presence of a mutation in B-Raf proto-oncogene, serine/threonine kinase (BRAF) [Ch 7q34, exon 15, V600E point mutation (c.1799T>A)]; telomerase reverse transcriptase (TERT) promotor mutation was negative (Ch 5p15.33, TERT C228T, C250T point mutation negative).

All four dissected central LNs were confirmed as



**Figure 1** Histopathological findings of PTC. (A) Gross examination of isthmus tumor. An ill-defined, firm, whitish mass with close resection margins (colored as blue ink). (B) Microscopic examination of papillary microcarcinoma revealed enlarged nuclei with clear chromatin, arranged in complex papillae with fibrovascular cores (H&E stain,  $\times 200$ ). (C) Extrathyroidal extension of tumor (H&E stain,  $\times 40$ ). (D) D2-40 immunohistochemistry highlights lymphatic emboli ( $\times 200$ ). PTC, papillary thyroid cancer; H&E, hematoxylin and eosin.

metastatic carcinomas without extranodal extension, and the largest metastatic deposit size was measuring up to 0.6 cm in diameter. According to the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) classification system, the pathological stage was determined as T1aN1aM0, stage I.

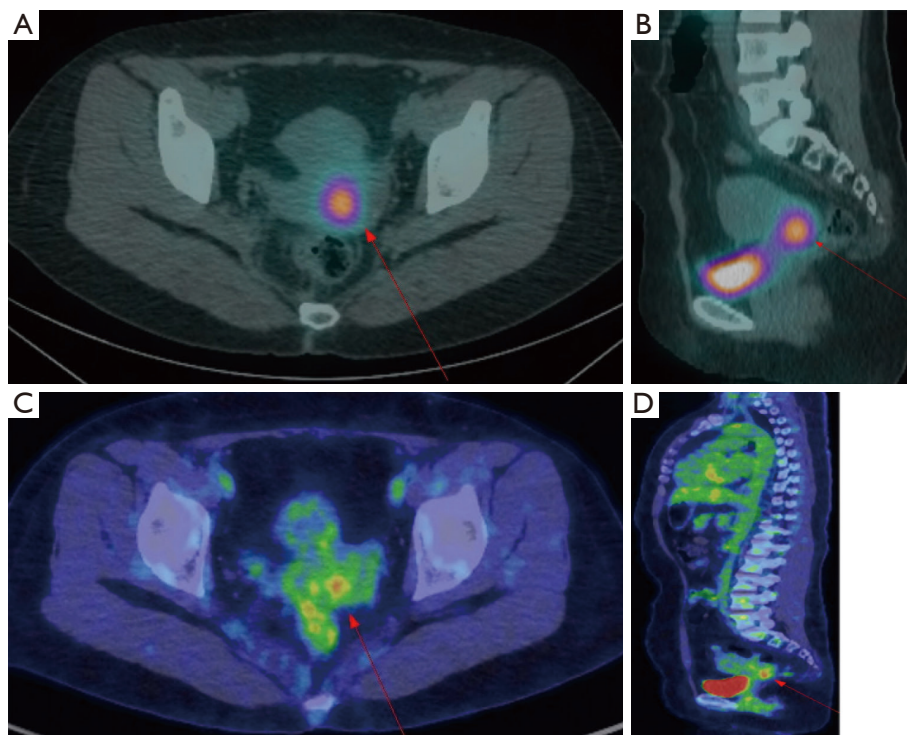
#### *Radioactive iodine (RAI) treatments after surgery—the first therapy*

Adjuvant RAI ablation treatment was indicated for the patient due to the presence of microscopic extrathyroidal extension, lymphovascular invasion of the tumor, and N1 disease involving LNs with 0.6 cm in largest dimension, which were the intermediate risk factors for disease recurrence according to the 2015 American Thyroid Association (ATA) risk stratification system. After 1 month of cessation of levothyroxine medication and exogenous stimulation with recombinant human thyroid stimulating hormone (TSH), she received RAI ablation treatment by administration of 150 mCi I-131 (postoperative 2 months). A WBS following therapeutic RAI ablation showed residual uptake in the thyroid bed alone.

Six-month follow-up neck US and chest computed tomography (CT) showed no recurrence. Two LNs (measuring 0.4 and 0.3 cm), which were seen in the left lower neck, level 6, were noted for close monitoring. The serum Tg level was 1.3 ng/mL, with a TSH level of 1.11  $\mu$ IU/mL (postoperative 8 months). The presence of measurable on-thyroxine serum Tg levels and the equivocal US findings indicated an incomplete response of RAI treatment. Additional RAI treatment was therefore determined.

#### *RAI treatments after surgery—the second therapy*

Second RAI ablation therapy was administered at a dose of 150 mCi after 2 months (postoperative 10 months). A WBS following therapeutic RAI ablation showed a focal uptake in the uterine cervix (Figure 2A,2B, arrows). Abdominopelvic CT and MRI showed no visible mass or abnormal signal intensity lesion in the cervix. An approximately 3.5 cm-sized septated thin-walled cyst in the left ovary was seen with contrast enhancement in the septum and wall. Fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}$ F-FDG PET/CT) was performed,



**Figure 2** Images of focal uptake in the uterine cervix at 11 months after total thyroidectomy for PTC. All arrows indicate the increased focal uptake in the uterine cervix. (A) Fused radioiodine SPECT/CT image in axial view. (B) Fused radioiodine SPECT/CT image in sagittal view. (C) Fused  $^{18}\text{F}$ -FDG PET/CT image in axial view. (D) Fused  $^{18}\text{F}$ -FDG PET/CT image in sagittal view. PTC, papillary thyroid cancer; SPECT/CT, single-photon emission computed tomography/computed tomography;  $^{18}\text{F}$ -FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography.

showing focal FDG uptake in the uterine cervix with an increased maximum standardized uptake value (SUVmax) of 4.1 (Figure 2C,2D, arrows). No other abnormal uptake was observed. The serum Tg level was 4.5 ng/mL, with a TSH level of 1.12  $\mu\text{IU/mL}$  (postoperative 11 months).

#### ***Discussion with the gynecology department for further treatment***

The patient was admitted to the gynecologic oncology unit. She had a gynecologic history of frequent vaginitis after cesarean section 8 years ago, but no abnormalities were observed in the gynecologic examination. Her serum carcinoembryonic antigen and cancer antigen 125 levels were 3.8 ng/mL and 16.3 U/mL, respectively, which were within normal range. The human papillomavirus Pap test was negative. Pelvis MRI showed no visible mass or abnormal signal intensity lesion in the uterine cervix, and a 3.5 cm benign-looking septate cyst in the left ovary was noted.

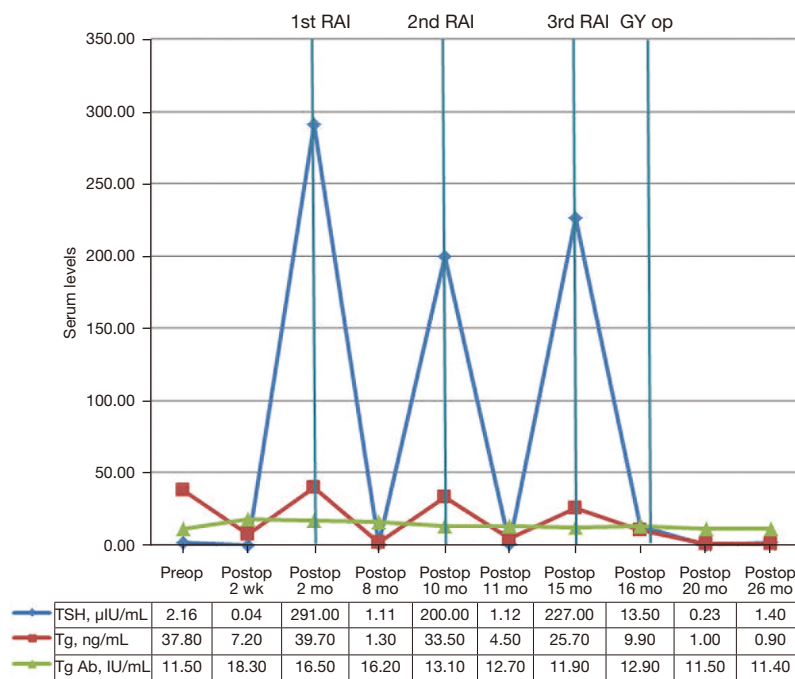
Cystography showed no demonstrable vesicocervical fistula.

Since there was no definite region of malignancy in the uterine cervix, the possibility of hidden malignancies in other regions should have also been considered. Instead of other options, additional RAI treatment with a follow-up WBS was first recommended. If the follow-up WBS showed persistent uptake in the uterine cervix, hysterectomy was proposed as one treatment option for the patient.

#### ***RAI treatments after surgery—the third therapy***

A third round of RAI ablation therapy was administered at a dose of 180 mCi (postoperative 15 months). The same focal uptake in the uterine cervix was observed on the posttherapeutic WBS. No uptake in other parts of the genitourinary tract was found. In addition, the new appearance of diffuse radioiodine uptake in the gallbladder led us to suspect inflammatory change.

Follow-up neck US and chest CT showed no evidence



**Figure 3** Serum level trends of TSH, Tg, and Tg Ab in the patient following total thyroidectomy. RAI, radioactive iodine; GY op, gynecologic operation; Preop, preoperative; Postop, postoperative; wk, week; mo, month; TSH, thyroid stimulating hormone; Tg, thyroglobulin; Tg Ab, thyroglobulin antibody.

of recurrence in the neck and the lung. Abdominopelvic CT revealed a 2 cm benign-looking cystic lesion in the left adnexa and a suspicious 1.9 cm intramural uterine myoma. Fundal adenomyomatosis of the gallbladder was noticed. The serum Tg level was 9.9 ng/mL, with a TSH level of 13.5  $\mu$ IU/mL (postoperative 16 months). Serial serum Tg and TSH levels of the patient are described in *Figure 3*.

### Gynecologic surgery and pathology

With no future plans for pregnancy and having a significant concern about the disease, the patient instantly decided to undergo further hysterectomy. Laparoscopic hysterectomy with bilateral salpingo-oophorectomy was performed, as scheduled (postoperative 17 months). There were no suspicious findings on gross examination of the uterine cervix; the uterine cervix was entirely embedded through a total of 19 blocks, but there was no evidence of metastatic lesions. Chronic cervicitis with squamous metaplasia, adenomyosis, and leiomyoma were diagnosed in the uterine specimen. No hidden malignancy was observed (*Figure 4*). The patient had an uneventful postoperative recovery.

After 3 months, follow-up abdominopelvic CT showed

persistent fundal adenomyomatosis of the gallbladder and no abnormalities suggestive of DM. Her serum Tg level was reduced to 1.0 ng/mL, with a TSH level of 0.23  $\mu$ IU/mL (postoperative 20 months) (*Figure 5*).

### The follow-up studies

Six months after the second surgery, the patient was in a good physical condition with no posttherapeutic complications and was eager to go through follow-up investigations to assess her disease status. The follow-up studies have shown a further decrease in the serum level of Tg to 0.9 ng/mL, with a TSH level of 1.4  $\mu$ IU/mL (*Figure 3*). Follow-up neck US showed no evidence of recurrence, and no abnormal uptake was seen in the  $^{18}$ F-FDG PET/CT (postoperative 26 months) (*Figure 5*). A benign cystic lesion in the right adnexa with no uptake was observed. A left ovarian cyst was not definitely seen. The patient was relieved with the results.

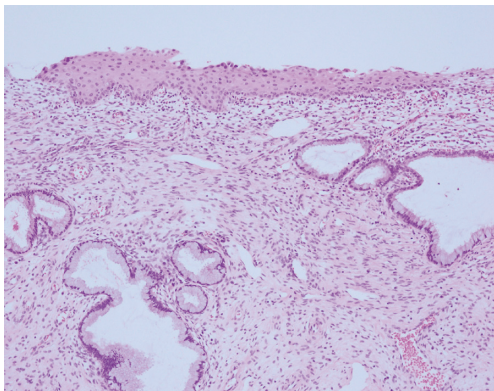
### Ethical statement

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.

## Discussion

PTC metastasis to the female genital tract is a rare event. Few cases have been reported including the involvement of the uterine myometrium, uterine corpus, and ovaries (9-11).



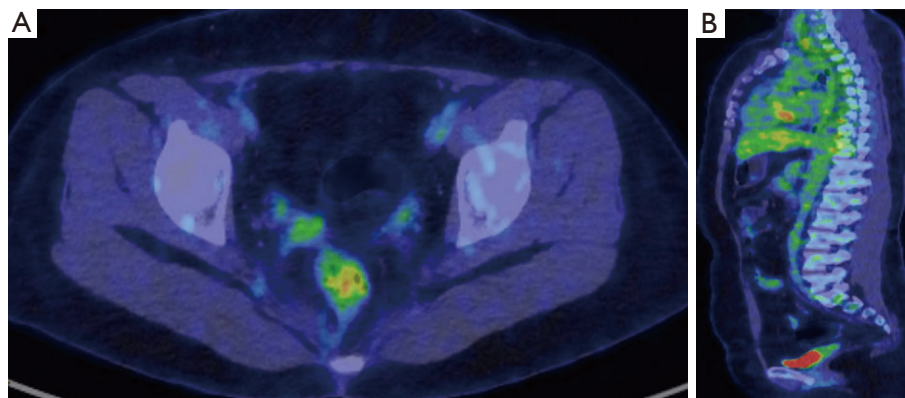
**Figure 4** Histological findings of uterine cervix with chronic nonspecific inflammation and squamous metaplasia (H&E stain,  $\times 100$ ). H&E, hematoxylin and eosin.

Metastasis to the uterine cervix is extremely unusual with no publication in the literature at this time. Occasional cervical metastases have been found in extragenital organ cancers, such as colorectal, stomach, and breast cancers (12).

With a significant negative impact on disease-specific survival and prognosis, DM of PTC should be considered a “possible occurrence at any time” which needs meticulous detection and aggressive treatment. This case had several “intermediate” risk factors for disease recurrence according to the 2015 ATA risk stratification system: minor extrathyroidal extension, lymphovascular invasion of the tumor, and N1 disease involving LNs (4 out of 4) with 0.6 cm in largest dimension. BRAF V600E mutation is associated with aggressive features and poor prognosis (13). Adjuvant RAI ablation treatment was indicated for the patient.

Serum Tg levels represent tumor burden and the capacity of the tumor to synthesize and secrete Tg. This marker is used to detect the recurrence of thyroid cancer after total thyroidectomy with or without RAI treatment (14). Patients with PTC who are considered clinically free of tumor have serum Tg levels  $< 1$  ng/mL with suppressed TSH (on-thyroxine).

In this case, elevated on- and off-thyroxine serum Tg levels indicated an incomplete biochemical response that led to a second and a third RAI ablation therapy (13). Moreover, posttherapeutic WBS and  $^{18}\text{F}$ -FDG PET/CT showed a preliminary finding of possible uterine cervix metastasis from PTC. After the third RAI ablation therapy, lasting uptake in the uterine cervix was seen, and serum



**Figure 5** Images of resolved uptake in the uterine cervix at 26 months after total thyroidectomy for PTC. (A) Fused  $^{18}\text{F}$ -FDG PET/CT image in axial view. (B) Fused radioiodine  $^{18}\text{F}$ -FDG PET/CT image in sagittal view. PTC, papillary thyroid cancer;  $^{18}\text{F}$ -FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography.

Tg was persistently elevated. After hysterectomy, negative imaging findings and decreased serum Tg levels ( $\leq 1$  ng/mL) were observed.

The diagnostic accuracy and pitfalls of imaging modalities should be carefully considered.  $^{131}\text{I}$  is the leading diagnostic and therapeutic agent for metastatic PTC. The combined results of posttherapeutic WBS and serum Tg testing can lead to the recognition of iodine avidity in the metastatic lesions, which is important in determining further treatment (15). The value of  $^{18}\text{F}$ -FDG PET/CT in PTC, which is known as an effective agent in detecting metastatic PTC lesions, especially in  $^{131}\text{I}$  WBS-negative, Tg-positive patients after RAI ablation, has also been demonstrated (16).

Regarding  $^{18}\text{F}$ -FDG uptake in the uterine cervix and its surgical pathology in our patient, the possibility of false positives should have been considered: from a gynecologic perspective,  $^{18}\text{F}$ -FDG uptake can originate from the physiologic renal excretion of FDG into the ureters and the urinary bladder, and increased FDG activity can occur in benign conditions such as uterine fibroids, pelvic inflammatory disease, and benign cystic lesions (17). Since vesicocervical fistula was not observed in this case, the inflammation in the cervix should have been considered together with PTC metastasis. Other study findings indicated that primary malignancy of the uterine cervix was less likely.

Although the patient had a history of frequent vaginitis after C-section delivery, she did not currently have vaginitis or other inflammatory changes. No specific threshold of SUVmax has been demonstrated to discriminate malignancy and inflammation of the cervix. One study reported a cut-off level of 4.0 as a higher probability of non-avidity to RAI in  $^{18}\text{F}$ -FDG-positive metastatic differentiated thyroid cancer (15). Our patient's SUVmax of  $^{18}\text{F}$ -FDG uptake in the cervix was 4.1, which was considered clinically significant.

Another possible explanation of elevated Tg levels with uptake in imaging studies is the presence of struma ovarii. There have been several cases of struma ovarii with similar clinical findings (18,19). Our patient also had ovarian cysts, which were noted on CT and MRI. However, no abnormal uptake in the ovaries was observed on WBS and  $^{18}\text{F}$ -FDG PET/CT. Furthermore, decreased serum Tg levels and negative imaging findings after hysterectomy would imply that the ovarian cysts were benign and far from being a form of struma ovarii.

Even though the final pathology did not confirm the uterine cervix metastasis, we should consider the possibility

of hidden malignancies in the uterine specimen. One study reported a hidden malignancy in asymptomatic uterine leiomyoma that was confirmed as PTC metastasis after surgical removal (20). In our case, we scrutinized the uterine specimen including the leiomyoma, but malignant cells were not identified. However, pathological examinations can be limited and cannot entirely exclude the microscopic metastatic spread to the other portions of the uterus. Since serum Tg levels were further decreased after hysterectomy, we postulate that further RAI ablation therapy with surgical resection was reasonable and not excessive.

Herein, we report a case of PTC with suspicious metachronous uterine cervix involvement. We acknowledge that cervix metastases of PTC are extremely rare, and the final pathology did not confirm metastasis from PTC. This case raises a discussion of differential diagnostic limitations in the setting of clinical and pathological investigations of PTC. Even though hysterectomy may be perceived as excessive treatment, the process leading to the conclusion of additional surgery was rational. Persistently elevated serum Tg levels with clear uptake in the cervix after repetitive high-dose RAI ablation following total thyroidectomy gave rise to reasonable suspicion of DM from PTC. Even with incomplete assurance of DM, our treatment strategies have resulted in the patient's decreased serum Tg levels, together with negative imaging findings. Based on the relevant rationales, through multidisciplinary discussion, this patient can ultimately obtain a better prognosis. Understanding the pitfalls of the imaging modalities and continuous efforts to overcome the limitations of the diagnostic process are crucial for future treatment.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gs-22-210/rf>

*Peer Review File:* Available at <https://gs.amegroups.com/article/view/10.21037/gs-22-210/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gs-22-210/coif>). The 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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