

Peer Review File

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Reviewer A

This study aims to report the case of an alleged metastasis of the cervix in papillary thyroid carcinoma due to increased thyroglobulin levels and uptake in the PCI in the pelvis.

This case described shows a young patient with papillary thyroid microcarcinoma with an incomplete biochemical response.

My considerations are:

Comment 1: Thyroglobulin dosing 2 weeks after Total Thyroidectomy is a confounder, ideally dosing after 12 weeks. I would remove it from the report because it has no value for decision making.

Response: We would like to thank the reviewer for the time and effort in reviewing our manuscript and providing comments and suggestions, which have considerably helped us improve the manuscript. We have answered each of the points below and hope that our responses and revisions address all the comments.

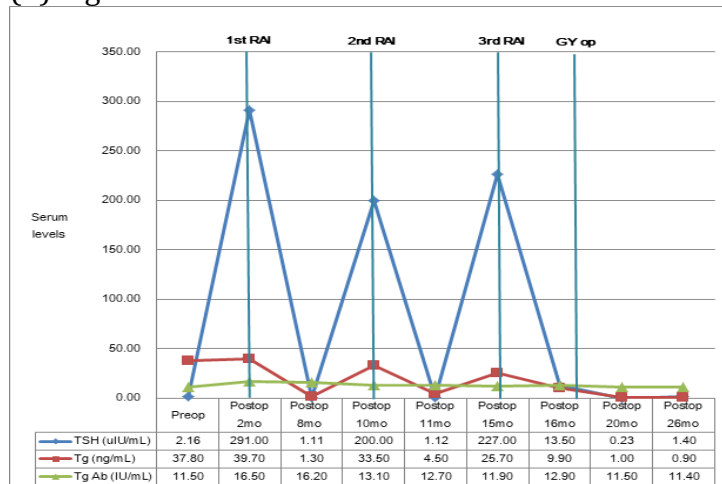
We appreciate the advice on the clinical insignificance of serum thyroglobulin (Tg) level at 2 weeks after total thyroidectomy. Following this, we have removed the text “the serum Tg and TSH levels at 2 weeks after total thyroidectomy” from Case presentation, page 6, lines 128-130. We have also removed the “serum Tg,” “Tg antibody,” and “TSH levels” from Figure 3.

Revised:

(a) “Radioactive iodine treatments after surgery – the first therapy” section in Case presentation

Adjuvant radioactive iodine (RAI) ablation treatment was indicated for the patient, owing 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 one month of cessation of levothyroxine medication and exogenous stimulation with recombinant human TSH, she received RAI ablation treatment by administration of 150 mCi I-131 (postoperative two months).

(b) Figure 3



Comment 2: The staging according to the TNM should be written, with recurrence risk stratification to justify the treatments performed. Clarify the criteria to justify RAI.

Response: We thank the reviewer for this comment. The pathologic stage of the tumor was T1aN1aM0, stage I, using the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis (TNM) staging system. According to the 2015 American Thyroid Association (ATA) risk stratification system, the disease was categorized as having an “intermediate” risk for recurrence due to the presence of minor extrathyroidal extension, lymphovascular invasion of the tumor, and N1 disease involving lymph nodes (4 out of 4) with 0.6 cm in largest dimension. Adjuvant radioactive iodine (RAI) ablation treatment was indicated for the patient. Prior to RAI treatment, thyroid hormone administration was withdrawn for one month and exogenous stimulation with recombinant human TSH (rhTSH) was administered. Following the reviewer’s comment, we have indicated the TNM staging and clarified the criteria for adjuvant RAI treatment in Case presentation, page 6, lines 124-126 and lines 128-132, respectively. We have added comments on the indication of RAI treatment in this case in the Discussion, page 10, lines 217-222. We have also commented on the use of rhTSH (page 6, line 133), which was based on ATA guideline B39, Recommendation 54, (B) [In patients with ATA intermediate-risk DTC who have extensive lymph node disease (multiple clinically involved LN) in the absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal prior to adjuvant RAI treatment.].

Added:

(a) “Pathology” section in Case presentation

All four dissected central LNs were confirmed as 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.

(b) “Radioactive iodine treatments after surgery – the first therapy” section in Case presentation

Adjuvant radioactive iodine (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 one month of cessation of levothyroxine medication and exogenous stimulation with recombinant human TSH, she received RAI ablation treatment by administration of 150 mCi I-131 (postoperative two months).

(c) DISCUSSION

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.

Comment 3: Classify the response to treatment - excellent response, or in this case, incomplete biochemical response.

Response: We appreciate the advice. Elevated on- and off-thyroxine serum Tg levels with equivocal imaging findings indicated an incomplete biochemical response that led to a second and a third RAI ablation therapy. We have added a sentence describing the incomplete response to RAI treatment in Case presentation, page 6, lines 139-141. We have also mentioned this in the Discussion, page 10, lines 227-228.

Added:

(a) "Radioactive iodine treatments after surgery – the first therapy" section in Case presentation

Six-month follow-up neck US and chest computed tomography (CT) showed no recurrence. Two LNs (measuring 0.4 cm 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 uIU/mL (postoperative eight months). **The presence of measurable serum Tg level while the patient was on thyroxine and the equivocal US findings indicated an incomplete response of RAI treatment. Additional RAI treatment was therefore determined.**

(b) Discussion

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 ¹⁸F-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 Tg was persistently elevated.**

Comment 4: On I-131 WBS, with the exception of physiological radioiodine uptake in the (salivary glands, stomach, and gastrointestinal and urinary tracts), lesions exhibiting radioiodine uptake can be considered to be metastatic. Therefore, it is imperative to carefully evaluate abnormal scans.

Uncommon findings have been reported, including ovarian masses. There are interesting cases of false-positive iodine uptake in the ovaries that was diagnosed as benign neoplasms or struma ovarii.

I request a review and clarification regarding the anatomopathological result of the ovarian cyst that was not described in the paper. Struma ovarii are ovarian cysts with thyroid tissue, with reports of serum thyroglobulin production, which could explain the uptake in WBS, the high levels of serum Tg, and the drop in these levels after gynecological surgery.

Response: We thank the reviewer for the considerate comment and kind request for further review. In fact, we have initially reviewed case reports of struma ovarii, which can explain our clinical findings during follow-up. However, no uptake was seen in the left and right adnexa in the second and third posttherapeutic whole-body scans (WBS). The recent follow-up studies of cases following "hysterectomy" showed decreased serum Tg levels with negative image findings in the FDG-PET scan. The PET scan report specifically commented on a cystic lesion in the right adnexa with "no" uptake, suggesting a benign feature. A left ovarian cyst that was found in the previous CT scan was not definitely seen in the study, and therefore was considered clinically insignificant. We have mentioned about the possible benign disease with uptake in the Discussion, page

11, lines 242-244.

According to the reviewer's comment, we have added descriptions of the negative uptake in the ovaries on the third posttherapeutic WBS (page 8, line 169) and the follow-up PET scan (page 9, lines 196-198). We have also mentioned struma ovarii as another possible explanation of these clinical findings in the Discussion, pages 11-12, lines 254-260.

Added:

(a) "Radioactive iodine treatments after surgery – the third therapy" section in Case presentation

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.

(b) "The follow-up studies" section in Case presentation

Follow-up neck US showed no evidence of recurrence, and no abnormal uptake was seen **in the ¹⁸F-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.

(c) Discussion

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 ¹⁸F-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.

Comment 5: Considering that there was no histological confirmation of metastasis in the uterus, there is no way to confirm that it was a uterine metastasis.

I suggest reassessing the data obtained or shifting the focus of the article from a case report of uterine metastasis to a false positive approach in follow-up imaging exams and the challenges for individualized treatment.

[Oikonomou, Christiana et al. "Recurrent Struma Ovarii Presented with High Levels of Thyroglobulin." Case reports in surgery vol. 2021 8868095. 22 Mar. 2021, doi:10.1155/2021/8868095

C. Ghander; D. Lussato; B. Conte Devolx; O. Mundler; D. Taïeb (2006). Incidental diagnosis of struma ovarii after thyroidectomy for thyroid cancer: Functional imaging studies and follow-up., 102(2), 378–380. doi:10.1016/j.ygyno.2006.01.047

¹Triggiani, Vincenzo; Giagulli, Vito Angelo; Iovino, Michele; De Pergola, Giovanni; Licchelli, Brunella; Varraso, Antonio; Dicembrino, Franca; Valle, Guido; Guastamacchia, Edoardo (2016). False positive diagnosis on ¹³¹Iodine whole-body scintigraphy of differentiated thyroid cancers. *Endocrine*, 53(3), 626–635. doi:10.1007/s12020-015-0750-3]

Response: We appreciate the reviewer's comments and recommendations. We have reduced the discussion on distant metastasis from PTC and added a text on the false positives and other possible explanations in the Discussion, using the

reviewers' references (pages 11-12, lines 254-269). Since the clinical findings provided reasonable suspicion of cervix metastasis, and we are hoping that there are some learning points in our management, we have managed to maintain the title of the manuscript.

Added:

(a) Discussion

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 ¹⁸F-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.

Reviewer B

Comment 1: The case report entitled "Papillary thyroid cancer with suspicious uterine cervix metastasis: case report and the literature review" described a rare clinical situation, however, the "suspicious" in title leaves readers wondering how to interpret the content.

Response: We deeply appreciate the reviewer's thoughtful review and comments. In this report, we present a patient with papillary thyroid cancer (PTC) who showed persistent uptake in the uterine cervix on the WBS and FDG-PET scan after total thyroidectomy and three adjuvant RAI therapies. With findings of persistently elevated serum Tg levels and absence of other abnormal uptakes, it was inevitable to clinically suspect PTC metastasis to the uterine cervix. After thorough discussion with the gynecology department, further treatment was determined based on the clinical "suspicion" of uterine cervix metastasis. We have considered and reviewed the manuscript text to explain this case. However, we assume that "suspicious" is the most appropriate word to describe the findings. If possible, we would be grateful to accept several recommendations from the reviewers that would make the title more suitable.

Moreover, we have revised the term in the Abstract (line 35) and Introduction (page 3, line 68) from clinical "diagnosis" to clinical "suspicion" to clarify our recognition of this case during the postoperative follow-up.

Revised:

(a) "Case Description" section in the Abstract

Even after three rounds of radioactive iodine ablation, persistently elevated serum thyroglobulin levels, combined with a suspicious finding in the whole-body scan and fluorodeoxyglucose positron emission tomography/computed

tomography, led to the clinical **suspicion** of uterine cervix metastasis from PTC.

(b) Introduction

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.

Comment 2: As described by the authors, the pathology of the final GYN operation did not yield malignant results, and the surgery was performed on a 38-year-old woman. The preoperative informed consent and postoperative explanation are perhaps the most interesting part in this case.

Response: We thank the reviewer for the comments. During follow-up, the patient was significantly concerned about her disease status and was eager to undergo further evaluation and treatment. Unlike the focal uptake in the uterine cervix on the WBS and FDG PET scan, the gynecologic examination and CT scan showed negative findings in the uterine cervix. An ovarian cyst and a uterine myoma were noted on the CT scan; thus, the possibility of hidden malignancies in other genital organs should have also been considered. Surgical removal was suggested for one option. Since the patient had no future plans for pregnancy and was very concerned about the disease, she herself instantly decided to undergo surgical removal. Since the ovarian cyst was considered as benign according to the imaging studies, hysterectomy was planned. Moreover, decreased on-thyroxine serum Tg levels and negative uptake in the cervix region after surgery significantly relieved the patient, even with negative pathologic findings, which we have mentioned in the manuscript. We have explained the possibility of hidden malignancies and mentioned that gynecologic surgery was only “proposed” by the gynecologic clinician in Case presentation, page 7, lines 161-165. We have also mentioned about the patient’s decision for further surgery on page 8, lines 179-180.

Added:

(a) “Discussion with the gynecology department for further treatment” section in Case presentation

Since there was no definite region of malignancy in the uterine cervix, the hidden malignancy 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.

(b) “Gynecologic surgery and pathology” section in Case presentation

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).

Comment 3: In addition, the article should be more chronological in description. What is the indication of each I-131? Just because Tg goes up?

Response: We appreciate the comments. We have specified each RAI therapy in the relevant section in Case presentation. We have added a comment on the indication of each RAI treatment. According to the 2015 American Thyroid Association (ATA) risk stratification system, the disease was categorized as having an “intermediate” risk for recurrence due to the presence of minor

extrathyroidal extension, lymphovascular invasion of the tumor, and N1 disease involving lymph nodes (4 out of 4) with 0.6 cm in largest dimension. Adjuvant radioactive iodine (RAI) ablation treatment was indicated for the patient. Six months after the first RAI treatment, the on-thyroxine serum Tg level was measurable and it was 1.3 ng/mL, and two equivocal LNs were seen on neck US. An incomplete response of the treatment was suspected, and additional RAI treatment was considered for the patient. The indications of the first and second RAI therapies are mentioned on page 6, lines 128-132, and page 6, lines 139-141, respectively. The third RAI therapy was recommended by both our department and the gynecology department, since the possibility of hidden malignancies was also considered and the occurrence of a primary gynecologic malignancy was less likely (page 7, lines 154-165).

Added:

(a) "Radioactive iodine treatments after surgery – the first therapy" section in Case presentation

Adjuvant radioactive iodine (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 one month of cessation of levothyroxine medication and exogenous stimulation with recombinant human TSH, she received RAI ablation treatment by administration of 150 mCi I-131 (postoperative two months).

(b) "Radioactive iodine treatments after surgery – the first therapy" section in Case presentation

Six-month follow-up neck US and chest computed tomography (CT) showed no recurrence. Two LNs (measuring 0.4 cm 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 uIU/mL (postoperative eight 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.

(c) "Discussion with the gynecology department for further treatment" section in Case presentation

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 hidden malignancy 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.

Comment 4: GYN surgery was performed one month after the last 180mCi I-131, how can the authors rule out the delayed effect of 3rd I-131? Did the authors consider performing GYN biopsy or alternative treatment (e.g. target therapy) before surgery?

Response: Since no focal region was found in the cervix during gynecologic examination and in the CT and MRI studies, gynecologic biopsy was not feasible for there was “no visible target,” and this was mentioned in the manuscript. Moreover, considerable uptake was only seen in the cervix and not in any other regions, which were considered as locally-advanced disease (PTC with localized metastatic region). Thus, localized treatments were first considered. Additional RAI treatment and further surgical removal were recommended for the patient, who instantly decided to undergo surgical removal after the third RAI therapy. Gynecologic surgery was performed as scheduled. This information is mentioned in Case presentation, page 7, lines 154-165, and page 8, 179-180.

Added:

(a) “Discussion with the gynecology department for further treatment” section in Case presentation

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 hidden malignancy 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.

(b) “Gynecologic surgery and pathology” section in Case presentation

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).

Comment 5: Also, the article length is too long and easy to lose focus. I would advise the authors to focus more on shared-decision making (SDM), and the value of this rare case report may be more highlighted.

Response: We appreciate the reviewer’s comment. We have reduced the Case presentation section and minimized the comments on distant metastasis from PTC throughout the manuscript. We have added the “Discussion with the gynecology department for further treatment” section in Case presentation, page 7, line 153-165. We have also mentioned more about false positives and other possible explanations of elevated Tg levels with uptake in the Discussion, pages 11-12, lines 254-269.

Added:

(a) “Discussion with the gynecology department for further treatment” section in

Case presentation

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 hidden malignancy 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.

(b) Discussion

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 ¹⁸F-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.

Reviewer C

Comment 1: The authors present a case report of papillary thyroid cancer with possible distant metastasis to the uterine cervix. This is an interesting case with an unanticipated and unsatisfying pathological report. One would assume that a metastatic deposit that is positive on both I131 and FDG PET (with resultant decrease in serum Tg) would have a correlating lesion on final pathology. Could the lesion been missed within the uterine leiomyoma, as seen in the below case report:

[Bertrand AS, Iannessi A, Peyrottes I, Lacout A, Thyss A, Marcy PY. Myoma Hot Spot: Tumor-to-Tumor Metastasis of Thyroid Origin into Uterine Leiomyoma. Eur Thyroid J. 2019 Oct;8(5):273-277. doi: 10.1159/000501153. Epub 2019 Jul 30. PMID: 31768339; PMCID: PMC6873082.]

Response: We deeply appreciate the reviewer's considerate comments and recommendation for further review. Unfortunately, even after the thorough examination, we could not find any malignant tissues in the entire uterine

specimen, including the uterine leiomyoma. We have mentioned the full examination of the uterine specimen in the manuscript and added comments on the possibility of hidden malignancies in Case presentation, page 8, lines 185-186. We have also mentioned the possibility of “missed” microscopic metastasis in other parts of the uterus in the Discussion (page 12, lines 261-267).

Added:

(a) “Gynecologic surgery and pathology” section in Case presentation

There were no suspicious findings on gross examination of the uterine cervix; the uterine cervix was entirely embedded through a total of nineteen 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).

(b) Discussion

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.

Comment 2: Line 69. Did surgical resection confirm the pathology? The authors describe the pathology as being equivocal.

Response: We thank the reviewer for the comment. Surgical resection confirmed the pathology of chronic cervicitis and no evidence of malignancy. However, decreased serum Tg levels and negative image findings after surgery provided insight into the case and some learning points. To clarify our aim of reporting this case, we have added a detailed description in Introduction, page 3, lines 69-72.

Added:

(a) Introduction

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.

Comment 3: Line 106. The use of “massive” is inappropriate. “Multiple clinically apparent central LN metastases” is probably better.

Response: We thank the reviewer for the advice. We have changed the word “massive” LN metastases to “multiple clinically apparent” central LN metastases on page 5, lines 105-106.

Revised:

(a) “Thyroid surgery” section in Case presentation

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.

Comment 4: Line 137. "...which should be distinguished from metastasis" is unclear.

Response: We thank the reviewer for the comment. We have removed the phrase from the text (pages 6-7, lines 144-145).

Revised:

"Radioactive iodine treatments after surgery – the second therapy" section in Case presentation

A WBS following therapeutic RAI ablation showed a focal uptake in the uterine cervix (Figure 2A, 2C).

Comment 5: Line 182-184. The placement of this phrasing seems out of place.

Response: Following this advice, we have removed the phrase from the text (page 9, lines 203-206).

Revised:

"The follow-up studies" section in Case presentation

All procedures performed in the study involving human participants 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.