

Peer Review File

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Reviewer A

Authors reported a case of incidentaloma of thyroid cancer with presenting metastatic cervical lymph node.

However, in Fig 1, ultrasound echography reveals a certain and obvious tumor. Or rather, it is hard that paratracheal lymph node is differed metastasis or not.

This case might be a minor thyroid tumor with paratracheal lymph node.

But pathological findings revealed that thyroid tumor is benign and that left paratracheal lymph node is involved of thyroid cancer.

This case is rare, worrisome and confused.

1) Did you perform fine needle aspiration to thyroid tumor and or cervical lymph node?

If you have done, this worrisome case might be elucidated or be diagnosed by cytology of those.

2) In discussion, you should mainly take up problem for not treatment but preoperative diagnosis of this case including the role of cytology. Because your treatment is not special in this case.

Comment 1: Did you perform fine needle aspiration to thyroid tumor and or cervical lymph node? If you have done, this worrisome case might be elucidated or be diagnosed by cytology of those.

Reply 1: Needle aspiration cytology of the thyroid and lymph nodes was recommended. However, the patient was anxious and refused to have a FNAB, requesting surgical excision instead. So, we didn't perform FNAB before surgery.

Changes in the text: We have added relevant statements, see Page 4, line 3-6.

Comment 2: In discussion, you should mainly take up problem for not treatment but preoperative diagnosis of this case including the role of cytology. Because your treatment is not special in this case.

Reply 2: Yes, thank you for your valuable advice. Indeed, there is nothing special about our treatment. Therefore, in the discussion section, we added Chinese guidelines and expert consensus recommendations to the article, explaining why we did not perform FNAB for thyroid and lymph nodes before surgery and performed direct surgery. Then we also deleted the discussion about routine treatment of papillary thyroid cancer.

Changes in the text: We have modified our text as advised, see Page 6, paragraphs 2.

Reviewer B

Lymph node metastasis without primary thyroid lesion is not very common. Although this report is interesting to me, I have some concerns.

- 1) Did the patient undergo fine needle aspiration to the thyroid nodule before operation? If so, what was the result?
- 2) Current guidelines including 2015 American Thyroid Association guidelines recommend not to perform thyroid surgery, in case of thyroid nodule <0.5cm. How about the guideline in China?

Comment 1: Did the patient undergo fine needle aspiration to the thyroid nodule before operation? If so, what was the result?

Reply 1: Needle aspiration cytology of the thyroid and lymph nodes was recommended. However, the patient was anxious and refused to have a FNAB, requesting surgical excision instead. So, we didn't perform FNAB before surgery. In the discussion section, we added Chinese guidelines and expert consensus recommendations to the article, explaining why we did not perform FNAB for thyroid and lymph nodes before surgery and performed direct surgery.

Changes in the text: We have added relevant statements, see Page 4, line 3-6.

Comment 2: Current guidelines including 2015 American Thyroid Association guidelines recommend not to perform thyroid surgery, in case of thyroid nodule <0.5cm. How about the guideline in China?

Reply 2: According to the 2012 Chinese guidelines for the diagnosis and treatment of thyroid nodules and differentiated thyroid cancers, surgical treatment is the first choice for most thyroid malignancies. The guidelines do not address the treatment of thyroid nodules smaller than 0.5cm. The expert consensus on the diagnosis and treatment of thyroid micropapillary carcinoma in China, released in 2016, acknowledged that controversy exists regarding whether intraglandular PTMC (especially under 5 mm in diameter) can be closely follow up without surgery. Surgical decision should be made after comprehensive analysis of the clinical stage of the tumor, risk assessment, and full communication with patients and their families. PTMC patients with the following conditions can also be considered for close observation and follow-up without surgery. First, non-pathological high-risk subtypes. Second, the tumor diameter is no more than 5mm. Third, the tumor is not close to the thyroid capsule and there is no surrounding tissue invasion. Fourth, there was no evidence of lymph node or distant metastasis. Fifth, no family history of thyroid cancer. Sixth, no history of neck radiation exposure during adolescence or childhood. Seventh, the patient has little psychological pressure and can actively cooperate with the follow-up. Close observation is recommended for patients who meet all seven conditions. Surgical treatment should be considered in the following cases during close observation: tumor diameter increased by more than 3 mm; Clinical metastasis was found. The patient changes his will and requests surgery.

Changes in the text: We have modified our text as advised, see Page 6, paragraphs 2.

Reviewer C

This is a very rare case that the tumor regression might have occurred. It is not the first reported case of thyroid carcinoma's regression, but I think this manuscript is interesting. I have some clinical questions.

Did you make a diagnosis of the lymph node metastasis before the surgery? If you did not, the clinical diagnosis before surgery was a suspect of papillary thyroid microcarcinoma (T1a N0 MX). Did you have an option of follow-up without surgery?

Any puncture aspiration cytology or blood thyroglobulin examination were performed before the surgery?

Page 5, Line 11; You commented the ectopic thyroid cancer. Did you examine areas other than the neck by CT scans.

There is a case report where the patient developed metastatic lymph node of papillary thyroid carcinoma with 1mm primary tumor.

(Occult Thyroid Carcinoma without Malignant Thyroid Gland Findings during Preoperative Examination: Report of Three Cases, <https://doi.org/10.1155/2020/4249067>)

That is similar to the current case. In that report, they said that total thyroidectomy should be considered even in the absence of malignant thyroid findings. You also commented the recommended treatment is total thyroidectomy (Page 5, Line 17). Did you consider the complementary thyroidectomy after the diagnosis?

Comment 1: Did you make a diagnosis of the lymph node metastasis before the surgery? If you did not, the clinical diagnosis before surgery was a suspect of papillary thyroid microcarcinoma (T1a N0 MX). Did you have an option of follow-up without surgery?

Reply 1: Needle aspiration cytology of the thyroid and lymph nodes was recommended. However, the patient was anxious and refused to have a FNAB, requesting surgical excision instead. So, we didn't perform FNAB before surgery. According to the 2012 Chinese guidelines for the diagnosis and treatment of thyroid nodules and differentiated thyroid cancers, surgical treatment is the first choice for most thyroid malignancies. The expert consensus on the diagnosis and treatment of thyroid micropapillary carcinoma in China, released in 2016, acknowledged that controversy exists regarding whether intraglandular PTMC (especially under 5 mm in diameter) can be closely follow up without surgery. Surgical decision should be made after comprehensive analysis of the clinical stage of the tumor, risk assessment, and full communication with patients and their families. PTMC patients with the

following conditions can also be considered for close observation and follow-up without surgery. First, non-pathological high-risk subtypes. Second, the tumor diameter is no more than 5mm. Third, the tumor is not close to the thyroid capsule and there is no surrounding tissue invasion. Fourth, there was no evidence of lymph node or distant metastasis. Fifth, no family history of thyroid cancer. Sixth, no history of neck radiation exposure during adolescence or childhood. Seventh, the patient has little psychological pressure and can actively cooperate with the follow-up. Close observation is recommended for patients who meet all seven conditions. However, our patient was anxious and requested surgical excision.

Changes in the text: We have added relevant statements, see Page 6, paragraphs 2.

Comment 2: Any puncture aspiration cytology or blood thyroglobulin examination were performed before the surgery?

Reply 2: Needle aspiration cytology of the thyroid and lymph nodes was recommended. However, the patient was anxious and refused to have a FNAB, requesting surgical excision instead. So, we didn't perform FNAB before surgery. We tested blood thyroglobulin preoperatively, and it was normal.

Changes in the text: We have added relevant statements, see Page 4, line 2-6.

Comment 3: Page 5, Line 11; You commented the ectopic thyroid cancer. Did you examine areas other than the neck by CT scans.

Reply 3: We didn't do a CT scan before surgery. But clinical physical examination, ultrasound, CT and blood examination were used to follow up the patient for 2 years. No tumor recurrence or metastasis was found, and no nodules were observed in the right thyroid gland or other areas of the neck.

Changes in the text: We have added relevant statements, see Page 5, line 8-11.

Comment 4: There is a case report where the patient developed metastatic lymph node of papillary thyroid carcinoma with 1mm primary tumor.

(Occult Thyroid Carcinoma without Malignant Thyroid Gland Findings during Preoperative Examination: Report of Three Cases, <https://doi.org/10.1155/2020/4249067>)

That is similar to the current case. In that report, they said that total thyroidectomy should be considered even in the absence of malignant thyroid findings. You also commented the recommended treatment is total thyroidectomy (Page 5, Line 17). Did you consider the complementary thyroidectomy after the diagnosis?

Reply 4: First of all, I would like to thank the reviewer for providing this reference article, which I also read carefully. Both we and the author mentioned the classification of occult thyroid cancer, which is divided into five categories:

Type 1 is sometimes found by autopsy or surgery for a benign lesion and is sometimes called latent cancer.

Type 2 is a papillary thyroid microcarcinoma (PTMC) detected accidentally, mainly by ultrasonography.

Type 3 is found with clinically apparent metastases of thyroid carcinoma, where the primary carcinoma is not detectable before surgery but is found in the final histological specimen.

Type 4 originates from an ectopic thyroid gland.

Type 5 has no carcinoma in the thyroid gland, only metastasis, also known as primary unknown cancer.

Of the three cases that Soji Toda et al. have encountered, patients with type 4 (cases 1 and 2)

originated from ectopic thyroid gland tissue, and with type 3 (case 3) in an occult thyroid cancer. In all three patients, preoperative examination highly suspected thyroid cancer metastasis and total thyroidectomy was performed. And our patient is different from these three. She belongs to type 5. Lymph node metastasis of thyroid cancer was not confirmed in preoperative examination and intraoperative frozen section, but papillary carcinoma metastasis was found in cervical lymph nodes in postoperative paraffin section. Therefore, we did not perform contralateral thyroidectomy in the first operation. Although right thyroid lobectomy was recommended, the patient refused and requested follow-up observation. No recurrence of the tumor was observed during a 2-year follow-up.

Changes in the text: We have added relevant statements, see Page 5, line 7-11.

Reviewer D

In a Case Report, the authors report on a young patient with a histologically confirmed lymph node metastasis of a papillary microcarcinoma without evidence of a primary disease after a hemithyroidectomy. In the follow-up described after two years, no tumor recurrence or tumor persistence were shown.

Various reasons such as errors in the pathological diagnosis, tumor regression, or ectopic thyroid tissue are listed as causes by the authors.

- In the patient's case, the indication for surgery was made primarily because of a suspicious thyroid nodule described by ultrasound. The cervical lymph nodes shown sonographically had a maximum size of 0.2 x 0.4 cm and were not described as clearly pathological. The operation was performed using left hemithyroidectomy and lymphadenectomy. The authors did not state the reasons for the lymphadenectomy. However, a lymphogenic metastasis was confirmed in the frozen section.
- The authors described that thyroidectomy with cervical lymphadenectomy and radioiodine therapy is the best choice for papillary thyroid carcinoma with lymphatic metastasis with good long-term results in their article. Then why was this not applied to the presented patient?
- Above all, the explanation of a spontaneous tumor regression is speculative - especially if the right thyroid lobe has not been histologically processed. A negative ultrasound does not rule out a papillary microcarcinoma.
- The suspicion of ectopic thyroid tissue cannot be ruled out either. A thyroid scan, which can detect ectopic thyroid tissue, cannot be performed if the right thyroid lobe is still in situ.

Overall, from my point of view, it is not possible to rule out a still existing thyroid carcinoma in the remaining thyroid lobe. Failure to perform a thyroidectomy significantly limits the informative value of the follow-up care. In addition, a thyroid scan could have excluded ectopic thyroid tissue if necessary. Only in this case, i.e. the definitive exclusion of a primary in the thyroid and the exclusion of ectopic thyroid tissue as a possible focus, can one speculate about errors in pathology or tumor regression or the like.

Comment 1: In the patient's case, the indication for surgery was made primarily because of a suspicious thyroid nodule described by ultrasound. The cervical lymph nodes shown sonographically had a maximum size of 0.2 x 0.4 cm and were not described as clearly pathological. The operation was performed using left hemithyroidectomy and lymphadenectomy. The authors did not state the reasons for the lymphadenectomy. However, a lymphogenic metastasis was confirmed in the frozen section.

Reply 1: Preoperative ultrasonography revealed a maximum of 0.4×0.2 lymph nodes in the neck, but no metastatic lymph nodes were identified. During the operation, the left thyroid lobule was excised first, and 2 hard nodules with unclear boundaries from the surrounding adipose tissue were found in the lymph node beside the thyroid gland. Considering that the sensitivity of preoperative ultrasound to assess lymph node metastasis has been reported to range from 10.9% to 30%, we performed a lymph node resection. Unfortunately, an intraoperative frozen section could not confirm a suspected papillary carcinoma metastasis to the lymph nodes. As a precaution, a preventive central lymph node dissection was performed.

Changes in the text: We have added relevant statements, see Page 7, line 20-22 and Page 8, line 1-6.

Comment 2: The authors described that thyroidectomy with cervical lymphadenectomy and radioiodine therapy is the best choice for papillary thyroid carcinoma with lymphatic metastasis with good long-term results in their article. Then why was this not applied to the presented patient?

Reply 2: Yes, thyroidectomy with cervical lymphadenectomy and radioiodine therapy is the best choice for papillary thyroid carcinoma with lymphatic metastasis. Further surgery to remove the right thyroid gland was recommended, but the patient refused, opting instead for observation and follow-up. Clinical physical examination, ultrasound, computed tomography (CT), and blood examinations were used to follow up the patient for 2 years. No tumor recurrence or metastasis was found, and no nodules were observed in the right thyroid gland.

Changes in the text: We have added relevant statements, see Page 5, line 7-11.

Comment 3: Above all, the explanation of a spontaneous tumor regression is speculative -

especially if the right thyroid lobe has not been histologically processed. A negative ultrasound does not rule out a papillary microcarcinoma.

Reply 3: Thanks for the reviewer's reminder. Indeed, spontaneous tumor regression is speculative in this case. Our representation is not very accurate. Our objective was to present a case of occult papillary carcinoma with lymph node metastasis and to review the literature on three possible hypotheses for this phenomenon.

Changes in the text: We have deleted relevant statements, see Page 9, line 21-22.

Comment 4: The suspicion of ectopic thyroid tissue cannot be ruled out either. A thyroid scan, which can detect ectopic thyroid tissue, cannot be performed if the right thyroid lobe is still in situ. Overall, from my point of view, it is not possible to rule out a still existing thyroid carcinoma in the remaining thyroid lobe. Failure to perform a thyroidectomy significantly limits the informative value of the follow-up care. In addition, a thyroid scan could have excluded ectopic thyroid tissue if necessary. Only in this case, i.e. the definitive exclusion of a primary in the thyroid and the exclusion of ectopic thyroid tissue as a possible focus, can one speculate about errors in pathology or tumor regression or the like.

Reply 4: There may be some deficiencies in our treatment, for example, FNAB was not performed before surgery. For example, right thyroid resection was recommended after surgery, but the patient also refused. As a result, we cannot determine the cause of occult thyroid cancer with lymph node metastasis, which also limits the informative value of the follow-up care. I should not speculate whether this case was due to spontaneous tumor regression or ectopic parathyroid gland. As I said before, our objective was to present a case of occult papillary carcinoma with lymph node metastasis and to review the literature on three possible hypotheses for this phenomenon. It is necessary to understand these rare clinical and pathological manifestations to avoid missed diagnoses.

Changes in the text: We have deleted relevant statements, see Page 9, line 21-22.
