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METASTATIC PAPILLARY THYROID CARCINOMA IN CERVICAL LYMPH NODES WITH AUTOIMMUNE THYROIDITIS AND NO PRIMARY TUMOR: CHALLENGING DIAGNOSIS AND MANAGEMENT OF A RARE CASE

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Abstract

Objective: Metastatic papillary thyroid carcinoma in the lymph nodes with no primary tumor in the thyroid gland and chronic thyroiditis on the background is rarely reported, easily missed and hardly recognized. We report the case of a 39-year-old female who was presented with no primary tumor in her both sides of thyroid gland and metastasis in the cervical lymph nodules.

Case presentation: According to preoperative examination, the patient was under levothyroxine treatment with autoimmune thyroiditis. The patient underwent a total thyroidectomy and lymph nodes dissection. Metastasis of papillary thyroid carcinoma was found in the central lymph nodes although there was no primary tumor in the thyroid gland after serial deep cut sections. After 2 years of follow-up, no metastasis of the tumor was found in this patient.

Result: Immunohistochemistry results showed metastatic lymph nodes were positive to thyroglobulin, galectin-3, HBME-1, cytokeratin 19 and negative for *BRAFV600E*, Ki-67 LI was >15%. Molecular analysis for *TERT* promoter mutations was negative.

Conclusion: Failure in identifying primary tumor may be attributed to the small size (<3 mm) and/or the extended fibrosis of thyroid. We believe attention should be paid to lymph nodes with no primary tumor with autoimmune thyroiditis in the background so as to avoid missed diagnoses and delayed treatment.

Keywords: *papillary thyroid carcinoma, cervical lymph node metastasis, occult thyroid carcinoma.*

Резюме

МЕТАСТАТИЧЕСКИЙ ПАПИЛЛЯРНЫЙ РАК ЩИТОВИДНОЙ ЖЕЛЕЗЫ В ШЕЙНЫХ ЛИМФАТИЧЕСКИХ УЗЛАХ ПРИ АУТОИММУННОМ ТИРЕОИДИТЕ И ОТСУТСТВИИ ПЕРВИЧНОЙ ОПУХОЛИ: СЛОЖНЫЙ ДИАГНОЗ И ВЕДЕНИЕ РЕДКОГО СЛУЧАЯ

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Введение: Метастатическая папиллярная карцинома щитовидной железы в лимфатические узлы без первичной опухоли щитовидной железы и на фоне хронического тиреоидита регистрируется редко, легко пропускается и трудно распознается. Мы сообщаем о случае 39-летней женщины, у которой не было первичной опухоли с обеих сторон щитовидной железы и метастазов в шейных лимфатических узлах.

Клинический случай: По данным предоперационного обследования пациент находился на лечении левотироксином по поводу аутоиммунного тиреоидита. Пациенту была проведена тотальная тиреоидэктомия и лимфодиссекция. Метастазы папиллярной карциномы щитовидной железы были обнаружены в центральных лимфатических узлах, после серии глубоких разрезов в щитовидной железе первичной опухоли не было. Через 2 года наблюдения метастазов опухоли у больной не обнаружено.

Результаты: результаты иммуногистохимии показали, что метастатические лимфатические узлы были положительными на тиреоглобулин, галектин-3, HBME-1, цитокератин 19 и отрицательными на *BRAFV600E*, Ki-67 LI составлял >15%. Молекулярный анализ на мутации промотора *TERT* был отрицательным.

Выводы: Неспособность идентифицирования первичной опухоли может быть связана с небольшим размером (<3 мм) и/или обширным фиброзом щитовидной железы. Мы считаем, что следует обращать внимание на лимфатические узлы без первичной опухоли на фоне аутоиммунного тиреоидита, чтобы избежать пропущенных диагнозов и несвоевременного лечения.

Ключевые слова: *папиллярный рак щитовидной железы, метастазы в шейные лимфатические узлы, скрытая карцинома щитовидной железы.*

Түйіндеме

АУТОИММУНДЫ ТИРЕОИДИТ КЕЗІНДЕГІ БІРІНШІЛІК ІСІКТІҢ ЖОҚТЫҒЫ ЖАҒДАЙЫНДАҒЫ МОЙЫН БӨЛІМІ ЛИМФА ТҮЙІНДЕРІНДЕГІ МЕТАСТАТИКАЛЫҚ ПАПИЛЛЯРЛЫ ҚАЛҚАНША БЕЗІНІҢ ҚАТЕРЛІ ІСІГІ: СИРЕК АУРУДЫ ДИАГНОСТИКАЛАУ ЖӘНЕ БАСҚАРУ

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Кіріспе: Мойын бөліміндегі қалқанша безінің метастаздық папиллярлы карциномасы қалқанша безінің біріншілік ісігінсіз және созылмалы тиреоидит негізінде сирек тіркеледі, ауыр анықталады. Біз қалқанша безінің екі жағынан да біріншілік ісігі болмаған және мойын бөлімінің лимфа түйіндеріне метастаз бермеген 39 жастағы әйел адамның жағдайын сипаттаймыз.

Клиникалық жағдай: Ота алдындағы зерттеу мәліметтері бойынша науқас аутоиммунды тиреоидит бойынша левотироксинмен ем қабылдауда болған. Науқасқа толық тиреоидэктомия және лимфодиссекция жүргізілген. Қалқанша безінің папиллярлы карциномасының метастаздары орталық лимфа түйіндерінде анықталған, қалқанша безіне жүргізілген бірнеше терең тілмелер біріншілік ісікті анықтамады. 2 жылдық бақылаудан кейін науқаста ісік метастаздары анықталмады.

Нәтижелер: Иммуногистохимия нәтижелері метастаздық лимфа түйіндері тиреоглобулин, галектин-3, HBME-1, цитокератин 19 оң және *BRAFV600E* теріс болғанын көрсетті, Ki-67 LI >15% болды. *TERT* промоторы мутациясына молекулалық анализ теріс нәтиже көрсетті.

Қорытынды: Біріншілік ісікті анықтай алмау ісіктің кіші мөлшерімен (<3 мм) және/немесе қалқанша безінің жайылмалы фиброзымен байланысты болуы мүмкін. Біздің ойымызша, аутоиммунды тиреоидит болған кезде диагнозды жіберіп алмау және емді кешіктірмеу үшін лимфа түйіндеріне біріншілік ісіксіз назар аудару керек.

Түйінді сөздер: *қалқанша безінің папиллярлы қатерлі ісігі, мойын лимфа түйіндерінің метастаздары, қалқанша безінің жасырын карциномасы.*

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Introduction

Well differentiated types, papillary and follicular thyroid carcinomas are most common thyroid cancer with overall excellent prognosis and disease specific survival is close to 100% if under age 20, however, elder age at diagnosis (≥ 55 years) is a poor prognostic factor, which has been included in the prognostic staging group of 2017 WHO classification [11]. Papillary thyroid carcinomas (PTC) can metastasize to the cervical lymph nodes and other distant sites. Thyroid carcinoma with lymph node papillary carcinoma metastasis but without a primary thyroid lesion is a rare phenomenon [9]. There is a growing number of PTC in the last 20 years due to increasing recognition of thyroid nodules on imaging (ultrasound and CT) [1]. And incidental ultrasound discovery of thyroid nodules is not uncommon. PTCs can metastasize to the cervical lymph nodes (5 - 20%) without involvement to prognosis and other distant sites (10 - 15%; lung, bones, CNS). Metastatic PTC in the lymph nodes with no primary tumor in the thyroid gland is rarely reported, easily missed and hardly recognized. A current case report describes metastatic PTC found in the cervical lymph nodes with no primary tumor in the thyroid gland.

Case presentation

A 39-year-old female was diagnosed with five cervical lymph nodes and no primary tumor in the thyroid gland. She did not present with fever, weight loss, or night sweats and no palpable mass in the physical examination. Her family, medical, and social history was unremarkable for thyroid cancer. The preoperative blood routine, and thyroglobulin test results were normal, thyroid-stimulating hormone (TSH) increased (85 mIU/mL (0.25-4)). The patient was under levothyroxine treatment with autoimmune thyroiditis. Neck ultrasonography showed some thyroid enlargement with inhomogeneous, hypoechoic, hypovascular echostructure and several enlarged lymph nodes of the central and lateral cervical compartment. Complex investigation including preoperative ultrasound examination revealed multiple hypoechoic nodules in the both lobes, with a largest size of about 0.4 cm × 0.3 cm, and no definite envelope-like echo. The lymph nodes were irregular in shape, hypoechoic in the periphery, and hyperechoic in the middle was suggestive of non-specific for reactive lymphadenitis. Cytology from the thyroid gland was concluded as suspicion for a follicular neoplasia. SPECT-CT of the neck and chest showed a focus of fixation in the projection of the lower third of the neck along the midline due to the inclusion of a radiotag in the altered paratracheal lymph nodes on the left (VI), 13x10x13 mm in size, and multiple small lymph nodes in the level II, IV, 6x2x5 mm in size. Conclusion of the endocrinologist is multinodular goiter with hypothyroidism, autoimmune thyroiditis. Patient underwent a total thyroidectomy with lymph node dissection for definitive surgical management. Eleven enlarged lymph nodes were found below the lower right and left lobe. The final pathological result of the paraffin section is no detectable primary tumor despite a full histologic examination of thyroid gland and metastatic papillary carcinoma was found in level II, IV, VI lymph nodes. Histology showed follicular neoplastic cells mainly arranged as macro and microfollicles with central colloid, focally branching papillae with fibrovascular cores, enlarged cells with nuclear enlargement, elongation and overlapping, chromatin margination (optically clear chromatin), ground glass nuclei, irregular nuclear membrane contour, nuclear grooves and no nuclear pseudoinclusions. Tumor was classified as papillary metastatic carcinoma with less papillary and predominant follicular architecture [11]. The thyroid tissue shows on the background moderate chronic thyroiditis showing lymphocytic infiltration with lymphoid follicle formation, focally atrophic thyroid follicles with abundant oncocytes but no reduced colloid, mainly consist of normal sized follicles, fibrosis exist but not extend beyond capsule and without squamous metaplasia. Focally psammoma bodies are found. Surgery was performed in Kazakh Institute of Oncology and Radiology, Almaty and follow-up treatment in the Center of Nuclear Medicine and Oncology, Semey, Kazakhstan. All specimens were sent to Nagasaki University, Department of Tumor and Diagnostic pathology, Japan, for further review, molecular and immunohistochemistry (IHC) analysis. Three pathologists (N.M., K.H., Z.M.) had examined the paraffin section carefully and found no detectable primary tumor despite a full histopathologic examination. In five lymph nodes metastatic papillary carcinoma were confirmed with the following immunohistochemistry: positive to thyroglobulin, galectin-3, HBME-1, cytokeratin 19 and negative for *BRAFV600E*, proliferation index Ki-67 was >15% (Fig 1). Molecular analysis for the presence of *TERT* promoter mutations (C228T, C250T) was negative. Based on the tumor, node, and metastasis (TNM) staging system [11], the patient's thyroid carcinoma stage was TxN1bM0, stage I.

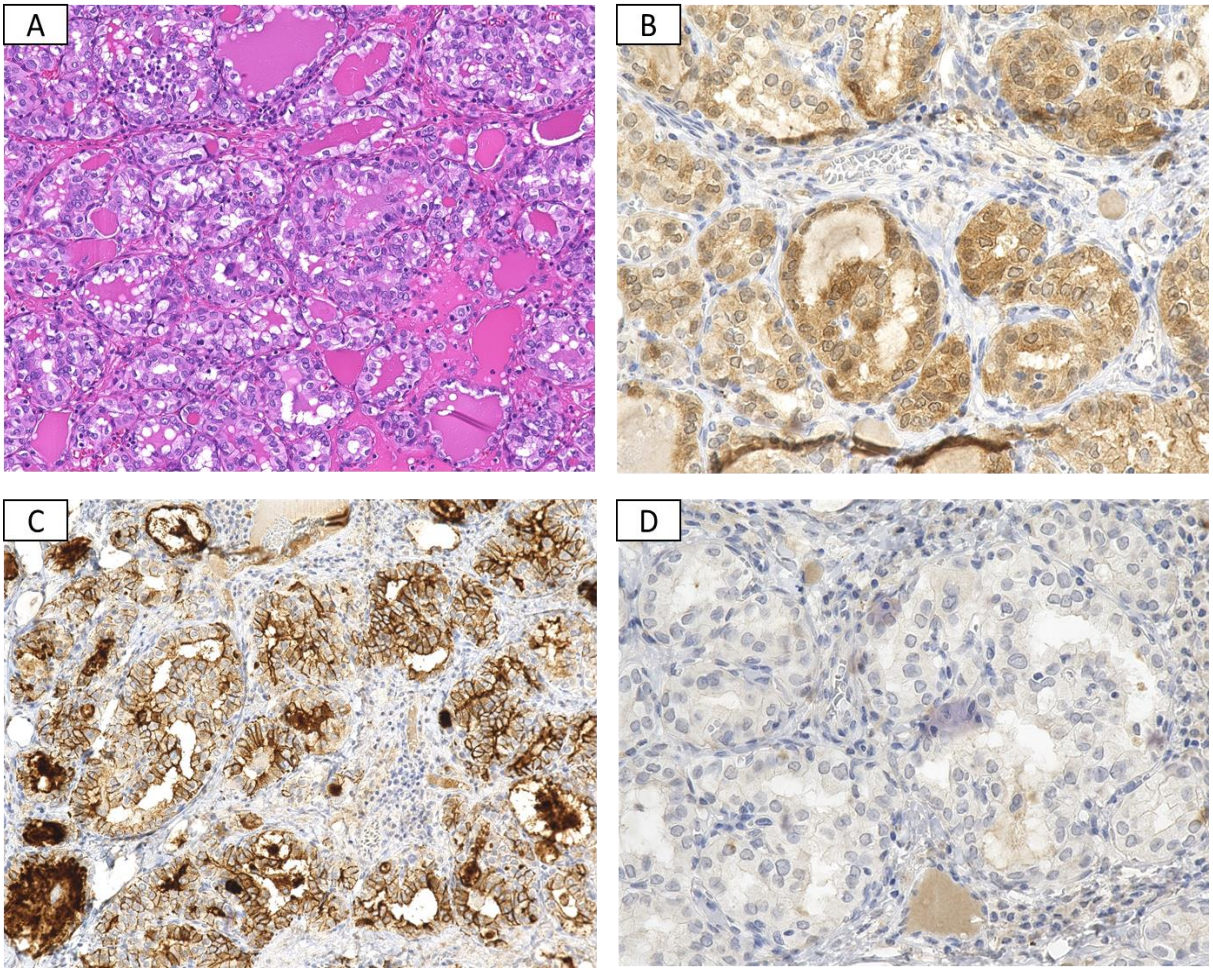

Figure 1. Histologic features of the cervical lymph nodule.
Histopathology revealed papillary thyroid cancer (A, hematoxylin-eosin, original magnification ×200).
Immunohistochemical stain showed positive to galectin-3 (B, original magnification ×400),
positive to HBME-1 (C, original magnification ×400), negative to *BRAFV600E* (D, original magnification ×400).

Patient received Iodine therapy with a single dose. Clinical physical examination, ultrasound, computed tomography, and blood examinations were used to follow up the patient for 2 years. No tumor metastasis was found. The patient recovered well without complications and was satisfied with the treatment and outcome. All procedures performed in studies 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 for publication of this case report and accompanying images.

Discussion

Occult thyroid carcinoma (OTC) was usually defined as an incidental disease, impalpable thyroid carcinoma, generally smaller than 1.0 cm in diameter, and it is called occult because it is usually detected at autopsy or during secondary surgery [12, 16]. Boucek et al. classified OTC into four different types [2]. The first type includes patients with benign thyroid disease who are incidentally diagnosed with thyroid cancer after a total thyroidectomy or at autopsy. The second type includes patients with papillary microcarcinoma of the thyroid that is found incidentally in imaging tests, such as ultrasound. The third type includes patients with clinically metastatic thyroid cancer, where the primary tumor is undetectable before surgery but is eventually found in histological specimens. The fourth type includes patients with thyroid cancer localized in ectopic thyroid tissue. Liu et al. presented the fifth type of OTC in which a thyroid gland lesion is diagnosed as benign according to pathological and imaging evaluations, but metastases of a thyroid carcinoma are detected in either locoregional lymph nodes or distant organs [10]. Patients in this fifth category were further classified into two groups. In the first, metastases of a thyroid carcinoma is detected in locoregional lymph nodes. In the second type, a distant organ metastatic mass is detected and diagnosed as metastasis from a thyroid carcinoma. In this report described the patient with the first group of the fifth type of OTC.

There are several possible hypotheses that could explain why a PTC would metastasize without a primary tumor in the thyroid gland. The first possible reason for the missed diagnosis is that the pathologist did not open all the thyroid tissue samples layer by layer and carefully examine them in accordance with the regulations, thereby missing the tumor tissue. If a lesion is smaller than 3 mm, it might be missed. Therefore, we should focus on the selection of fibrous scar tissue or gray nodules [9].

Another hypothesis is spontaneous regression of a tumor is defined as the partial or total disappearance of a tumor when it has not been treated at all, or it has been insufficiently treated. The estimated incidence of tumor regression is about 1 in 140,000 [4]. By studying 176 cases

of the spontaneous regression of cancer, Cole found that stimulation of the immune process is the most important factor in the spontaneous regression of cancer. There are many stimulating factors, including bacterial products, enzymes, infection, hormones, and trauma [3]. Co-occurrence of chronic thyroiditis and PTC is found in 23-30% and the presence of autoimmune thyroiditis is considered a favorable prognostic factor. The association between PTC and autoimmune thyroiditis remains unclear [8]. The immune system also plays an important role in the clinical evolution of PTC. In PTC, phagocytosis of tumor cells by macrophages has been identified and is associated with an increased incidence of lymph node metastasis, extra-thyroid infiltration, and distant metastasis [6]. Thus, fibrosis may be a sign of partial or complete tumor regression in thyroid cancer or may be a cause of this rare phenomenon. In some cases where fibrosis is very extensive, tumor cells are rarely found [7]. Simpson analyzed the histological and clinical features of 2 cases of thyroid papillary microcarcinoma, one with a diffuse sclerosis variant and the other with a multicellular follicular variant, both of which suggested partial tumor regression [15]. Nishikawa et al. reported a case of primary occult PT with bone metastasis, but only diffuse dense fibrosis with lymphocytic infiltration was found in the thyroid gland, and no primary thyroid lesion was detected. It has been suggested that some occurrences of primary occult PTC may subside or disappear after distant metastasis due to immunity or other host resistance factors [13].

In addition, PTC may occur in ectopic thyroid tissue. An ectopic thyroid is a congenital developmental disorder. It can be located along the embryonic migration path of the thyroid gland, from the foramen cecum to the anterior mediastinum [14]. Ectopic thyroid tissues located in the kidney, heart, gallbladder, and pancreas have also been reported [5]. It is possible that carcinoma can develop in the ectopic thyroid tissue and then metastasize to the locoregional lymph nodes or distant organs while the thyroid itself remains normal.

Conclusions. We described a rare case of lymph node thyroid carcinoma with no primary tumor. The possible explanations for failure in identifying primary tumor may be attributed to the small size (<3 mm) and tumor lesion being missed on histological examination, tumor regression, and ectopic thyroid carcinoma. It is necessary to pay attention to these rare clinical and pathological manifestations to avoid missed diagnoses and delayed treatment.

Authors contributions:

Mussazhanova Zh., Targynova A. carried out the molecular genetic studies.

Mussazhanova Zh., Targynova A drafted the manuscript.

Mussazhanova Zh., Targynova A., Mukanova A., Kaidarova S., Shalgimbayeva G., Madiyeva M., Pak L., Zhabagin K., Belikhina T., Rakhimzhanova G, Yeleubayeva Zh., Bolsynbekova S., Kalmatayeva Zh., Issayeva R., Sarsenova L., Umirova R., Nakashima M. participated in the diagnosis and interpretation of immunoassays.

Nakashima M. conceived of the study and participated in coordination and helped to draft the manuscript.

All authors have read and approved the final version to be published.

Competing interests: The authors declare that they have no competing interests.

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