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PSAMMOMA BODIES IN LYMPH NODES OF THE NECK: POSSIBLE PRECURSOR OF LOCOREGIONAL METASTASES OF PAPILLARY THYROID CARCINOMA

Background. Papillary thyroid carcinoma (PTC) is the most common type of well-differentiated thyroid cancer accounting for up to 80% of all thyroid neoplasms. Metastases to the regional lymph nodes (RLN) of the neck are a feature of its biological aggressiveness. The presence of psammoma bodies may be considered a pathomorphological feature of PTC in addition to the papillary structure of tumor and specific nuclear changes. The aim of the study was to evaluate a clinical value of psammoma bodies in the RLN of PTC patients. Materials and Methods. 91 patients with PTC who were surgically treated at the Verum Expert Clinic were enrolled in the study. The clinical and pathomorphological data were retrieved from the archival medical records. Results. According to the results of the clinico-morphological analysis, 51 patients (56%) with PTC had metastases in the RLN of the neck, and 40 (44%) patients had no metastases. Among 51 patients with metastases in the RLN, in 4 patients psammoma bodies in the RLN and tumor tissue were identified. In 3 of these 4 patients, the size of the primary PTC tumor was less than 10 mm, but an aggressive cancer course such as significant number of metastases in the RLN or multifocal growth was found in all these cases. Conclusions. The presence of psammoma bodies in RLN and primary PTC tumor could be suggested as a predictor of metastasis to lymph nodes. The detection of point echogenic foci in the lymph nodes by ultrasound at the preoperative stage is a sign of psammoma bodies. This finding can be useful for improving the efficacy in selection of surgical treatment tactics for the optimal neck dissection by planning neck dissection in the presence of such point echogenic foci at the preoperative stage and performing regular check-ups of the patients.

Keywords: papillary thyroid carcinoma, metastases in locoregional lymph nodes, psammoma bodies.

Papillary thyroid carcinoma (PTC) is one of the most common types of differentiated thyroid cancer, accounting up to 80% of all thyroid neo-

plasms [1, 2]. In most cases, PTC is characterized by an excellent prognosis (95%—99%), but certain cases might be present with metastases to the re-

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gional lymph nodes (RLN), which is a manifestation of the biological aggressiveness of the tumor [3, 4]. However, RLN are not always identified preoperatively during ultrasound examination or macroscopic evaluation while performing surgery. Moreover, in 20-50% of cases, metastases in the lymph nodes are detected during the final pathohistological examination after a negative result of the frozen section [5-7]. Most often, PTC metastases are localized in the 6th collector, which necessitates prophylactic dissection of this anatomical area. One of the pathomorphological features of PTC is the presence of psammoma bodies, which is an additional microscopic feature of the PTC besides nuclear features [8, 9]. Psammoma bodies represent concentric layering of calcified plates, which form spherical structures with clear edges and are characterized by a basophilic staining. Psammoma bodies differ from the areas of dystrophic calcification, as the latter is characterized by uneven contours and there are no signs of layering of plates. The mechanism of the formation of psammoma bodies has not been thoroughly studied. According to one hypothesis, they occur because of necrosis and calcification of the tumor thrombi in the vessels. Nevertheless, the clinical significance of this pathomorphological anomaly has been studied by many authors [10] Although psammoma bodies can also be determined in multinodular goiter, they are more often associated with PTC. According to the results of the published studies, the presence of psammoma bodies is considered as a sign of an unfavorable prognosis of PTC such as multifocal growth, bilateral lesions, and metastases [11]. The detection of psammoma bodies in the lymph nodes may be a pathomorphological sign of PTC metastasis, even in the absence of tumor deposits in the lymph nodes and requires additional analyses and serial sections of lymph node tissue during the final pathohistological examination [12]. The clinical and prognostic value of psammoma bodies in PTC remains a controversial issue, especially considering their association with an unfavorable prognosis. Therefore, further studies of this pathomorphological feature in PTC are important in view of resolving the possibility of preoperative diagnosis.

The aim of the study was to evaluate the clinical value of psammoma bodies in patients with PTC.

Materials and Methods

This study analyzed the results of surgical treatment of 91 patients with PTC. The patients underwent surgical treatment at the Verum Expert Clinic. The clinical and morphological characteristics of the patients were obtained from the medical records. The preoperative examination of patients including the hormonal status, clinical chemistry test, biochemical blood tests, and ionized calcium were performed as described in our previous publications [13-16]. All patients underwent ultrasound examination of the thyroid gland using the TIRADS classification [17]. A fine-needle aspiration biopsy (FNA) was performed in all patients with focal pathology of the thyroid gland, followed by the cytological verification according to the Bethesda classification (TBSRTC categories) [18]. A detailed description of the applied clinical approaches has been given in our previous studies [19-21]. In brief, the capsular dissection technique was used for thyroidectomy, and central neck dissection was performed in all patients with verified PTC. The operative and postoperative treatment was carried out taking into account international and local recommendations [2, 22]. I¹³¹ ablation was prescribed after thyroidectomy for the patients with the presence of extrathyroidal invasion or metastases. The final pathohistological examination was performed in accordance with the WHO classification of endocrine tumors [23].

Results

According to the results of the clinical and morphological analysis, 51 patients (56%) with PTC had metastases in the neck RLN, and 40 (44%) patients had no metastases. Among 51 patients with RLN metastases, psammoma bodies were found in lymph nodes and tumor tissue of 4 patients. The studied clinical and pathomorphological characteristics of these patients are shown in Table 1.

Data analysis of these 4 patients also showed the presence of lymph nodes in which no metastatic deposits of PTC were detected but only psammoma bodies were present (Figs. 1 and 2). The clinical and pathomorphological characteristics of these patients showed similarity of most parameters (Table 2).

The mean age of the patients at the time of surgery was 34 years. An analysis of the ultrasound

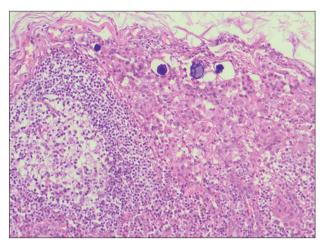


Fig. 1. Microscopical view of the metastasis of PTC to a locoregional lymph node with psammoma bodies in the subcapsular area. Hematoxylin-eosin staining, ×880

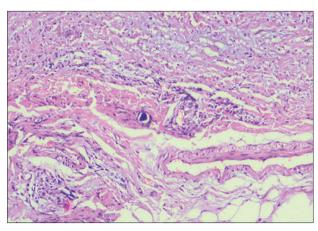


Fig. **2.** Microscopical view of the metastasis of PTC to a locoregional lymph node with evidence of the extranodal extension in the presence of psammoma bodies. Hematoxylin-eosin staining, ×880

Table 1. Clinical and pathomorphological characteristics of PTC patients with metastases in the neck RLN and psammoma bodies in the lymph nodes

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	
Gender	Female	Female	Female	Female	
Age at diagnosis (years)	31	20	38	48	
TIRADS	4	4	4	3	
Cytology category by Bethesda	6	6	5	6	
Surgery (TE — thyroidectomy)	TE	TE	TE	TE	
Dissection of the neck compartment	Central	Central	Central	Central and left lateral	

Table 2. Pathomorphological parameters of PTC patients with metastases in the neck RLN and psammoma bodies in the lymph nodes

Parameters	Patient 1	Patient 2	Patient 3	Patient 4
Tumor size, cm	0.8	1.5	0.9	0.6
PTC accompanied with other thyroid pathologies	Yes	No	Yes	Yes
Multifocality	Yes	No	No	No
Resection margin	R0	R0	R0	R0
Invasion to blood vessels	No	No	No	No
Invasion to lymphatic vessels	Yes	Yes	Yes	No
Perineural invasion	No	No	No	No
Mitosis figures in 10 high power fields (400x)	0	0	0	0
Microscopic extrathyroidal invasion	0	0	0	0
Macroscopic extrathyroidal invasion	0	0	0	0
Metastases to RLN	Yes	Yes	Yes	Yes
Number of evaluated lymph nodes/lymph nodes				
with metastases	16/2	11/5	18/6	13/1
Size of metastatic deposit, mm	0.05	2.5	0.5	0.5
Extranodal extension	No	Yes	No	No
PTC recurrency	No	No	No	No

data by the TIRADS classes showed a predominance of class 4 (3/4), which corresponds to a high risk of malignancy. The TIRADS data were also consistent with a relatively equal frequency of TBSRTC categories 6 (3/4) of cytological findings according to the Bethesda system. All patients underwent thyroidectomy and neck dissection, and organ-preserving operations were not performed (Table 1). It should also be noted that in 3 out of 4 patients, the size of the primary tumor was less than 10 mm but regardless of the tumor size, an aggressive cancer course with a significant number of metastases in the RLN or multifocal growth was found in these cases.

An adequate number of lymph nodes (on average 11 lymph nodes) were excised, some of which were affected by PTC metastases, while lymph nodes without obvious signs of metastases but with deposits of psammoma bodies were also identified (Table 2). The analysis of these data points to the ambiguity of the clear presence of metastasis in one patient, since the deposits of psammoma bodies are an indirect histological sign of PTC metastasis. In each case, a multidisciplinary council decided on further treatment tactics; all patients were prescribed for radioiodine ablation.

Discussion

This study analyzed cases of PTC with metastases in the RLN with psammoma bodies in some lymph nodes as well as the metastatic deposits. According to the literature, the presence of psammoma bodies due to PTC may indicate a tendency to metastatic spread in the RLN of the neck and casuistically be a factor in myocardial tamponade [9, 11, 24].

We have presented clinical cases of patients who simultaneously had lymph node metastases of PTC and the deposits of psammoma bodies along with one case with the deposits of psammoma bodies in a lymph node. This study continues the debate regarding the clinical management of PTC cases in which there are no reliable signs of PTC metastasis but there are deposits of psammoma bodies, which may be an indirect histological sign of PTC metastasis. In such cases, a clinical dilemma arises regarding the stratification of patients according to PTC risk groups, the appointment of radioiodine therapy, or clinical observation. Our data

showed that 3 of 4 patients had a combination of histologically verified PTC metastases to the RLN and lymph nodes with the deposits of psammoma bodies. At the same time, one case with only deposits of psammoma bodies may indicate early detection of PTC, even before the formation of histologically reliable metastases of PTC. We also agree with Chernock et al. [25] that the deposits of psammoma bodies may indicate the presence of a very small number of PTC cells, which are not detected by microscopy, or the possible presence of metastases in the deeper layers of the paraffin block, which must be taken into account during pathohistological examination.

By Kurochkin et al. [26], the presence of psammoma bodies with no detection of a tumor in the thyroid may indicate a latent course of the disease and possible PTC microcarcinoma, which is consistent with the results of our research (3 of 4 cases were PTC microcarcinomas with aggressive biological characteristics). The results of our study confirm the data of Bahcecioglu et al. [27] who demonstrated the significance of the presence of psammoma bodies in a large cohort of patients and proved the role of ultrasound diagnostics in the identification of echogenic formations in the lymph nodes that later corresponded to psammoma bodies during the final pathohistological examination. In the work of Luo et al. [28], who demonstrated a model of preoperative assessment of metastases in the central collector of the neck in PTC on the clinical material of 1714 patients using ROC analysis, an increased risk of metastases was shown in the presence of punctate echogenic foci <1 mm which subsequently corresponded to psammoma bodies during the final histopathology. The authors also showed the risk of metastasis in the presence of psammoma bodies at the level of 2.441 and multifocality at the level of 2.263, which is also consistent with our observations. These results support the importance of considering hyperechoic inclusions preoperatively as evidenced by TIRADS class 4 in our patients with psammoma bodies. Similar data regarding the possible role of preoperative punctate echogenic foci were demonstrated by Liu et al. [6] in a large cohort of 966 patients. Wei et al. [29] demonstrated the role of the presence of microcalcifications (punctate echogenic foci) preoperatively in a large cohort of patients with PTC microcarcinoma (710 patients). In our study, the majority of patients were identified as TIRADS class 4, albeit with carcinoma less than 1 cm in size (i.e., PTC microcarcinoma). All these results support our hypothesis regarding the need to consider punctate echogenic foci during preoperative examination, which may be later diagnosed as psammoma bodies, which is consistent with the results of other studies [30]. It is worth mentioning that Bai et al. [10] indicated the clinical significance of the presence of psammoma bodies and other variants of stromal calcification in PTC. According to them, psammoma bodies are a reliable predictor of PTC, which correlates with a higher frequency of locoregional metastases and a tendency to extrathyroidal invasion. A significant factor is also the poorer survival rate in patients with PTC in the presence of psammoma bodies [10]. Another evidence of an unfavorable clinical course in PTC patients with psammoma bodies is the higher recurrence rate, as shown in the study by Carcangiu et al. [31], which was also confirmed by Gubbiotti et al. [32] showing a higher frequency of tumor emboli in lymphatic capillaries in the presence of psammoma bodies. Both studies emphasized the importance of noting this sign in pathohistological conclusions [31, 32]. It is also worth mentioning that Cardisciani et al. [9] and Bai et al. [3] have suggested a worse clinical course of patients with psammoma bodies as compared to those indi-

viduals without this pathohistological feature. In our opinion, it is important to continue stuides on the larger cohort encompassing metastatic subgroups of patients with/without psammoma bodies.

We have performed this research on 91 cases with PTC, however psammoma bodies were identified only in 4 patients, which might be considered as a limitation due to the relatively small number of cases. However, such a limitation might be explained by the relatively infrequent diagnosis of psammoma bodies.

To sum up the presence of psammoma bodies in lymph nodes and PTC tumor could be considered a predictor of metastasis to lymph nodes, which is one of the parameters of the biological aggressiveness of tumor. The detection of point echogenic foci by ultrasound at the preoperative stage in the lymph nodes is a sign of psammoma bodies, which points on the necessity to increase efficiency in the choice of surgical treatment tactics for the optimal neck dissection and to perform regular follow-up of the patients.

Further investigations in larger cohorts are needed to determine the prognostic role of psammoma bodies in lymph nodes for better risk stratification for PTC patients. The future studies should also consider whether or not to prescribe the radioiodine ablation for patients with PTC and psammoma bodies in the lymph nodes without evidence of PTC metastases.

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ПСАМОМНІ ТІЛЬЦЯ В ЛІМФОВУЗЛАХ ШИЇ: МОЖЛИВИЙ ПЕРЕДВІСНИК ЛОКОРЕГІОНАРНОГО МЕТАСТАЗУВАННЯ ПАПІЛЯРНОЇ КАРЦИНОМИ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Стан питання. Папілярний рак щитоподібної залози (ПРЩЗ) є однією з найпоширеніших форм диференційованого раку щитоподібної залози і складає понад 80% усіх випадків. Метастази в регіонарні лімфатичні вузли шиї ПРЩЗ є проявом біологічної агресивності пухлини. Однією з патоморфологічних особливостей ПРЩЗ, окрім папілярної будови та характерних ядерних змін, є наявність псамомних тілець. Мета дослідження. Оцінити клінічну цінність псамомних тілець у регіонарних лімфатичних вузлах пацієнтів із ПРЩЗ. Матеріали та методи. У цьому дослідженні проаналізовано результати хірургічного лікування 91 хворого з ПРШЗ у клініці Verum Expert Clinic. Клінічні дані та дані патоморфологічних досліджень ідентифіковано з архівних медичних документів. Результати. Згідно з результатами клініко-морфологічних досліджень, у 51 пацієнта (56%) з ПРШЗ виявлено метастази в регіонарні лімфовузли шиї, а в 40 (44%) пацієнтів метастазів не виявлено. Серед 51 пацієнта з метастазами в лімфатичні вузли, у 4 пацієнтів виявлено псамомні тільця в лімфатичних вузлах та тканині пухлини. У трьох із чотирьох пацієнтів розмір досліджуваної пухлини ПРШЗ був менше 10 мм, але, незважаючи на розміри, у цих випадках виявлено агресивний біологічний перебіг пухлини — суттєва кількість метастазів в регіонарних лімфовузлах або мультифокальний ріст. Висновки. Наявність псамомних тілець в лімфатичних вузлах та пухлині ПРЩЗ слід розглядати як предиктор метастазування в лімфатичні вузли, що є одним з параметрів біологічної агресивності карциноми. Виявлення точкових ехогенних вогнищ за допомогою УЗД на передопераційному етапі в лімфатичних вузлах є ознакою наявності псамомних тілець, що дозволяє підвищити ефективність у виборі тактики хірургічного лікування щодо оптимальної дисекції шиї, планувати проводити дисекцію шиї за наявністю точкових ехогенних вогнищ на передопераційному етапі та регулярно проводити чекапи пацієнтів під час клінічного спостереження.

Ключові слова: папілярна карцинома щитоподібної залози, метастази в локорегіонарні лімфовузли, псамомні тільця.