РОЛЬ ПРИЦЕЛЬНОЙ ТОНКОИГОЛЬНОЙ АСПИРАЦИОННОЙ БИОПСИИ СО СМЫВОМ НА ПАРАТГОРМОН В ТОПИЧЕСКОЙ ДИАГНОСТИКЕ ИНТРАТИРЕОИДНЫХ ПАРААДЕНОМ ПРИ ПЕРВИЧНОМ ГИПЕРПАРАТИРЕОЗЕ

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Сложности в топической диагностике первичного гиперпартиреоза в ряде случае обусловлены вариабельностью расположения околощитовидных желез. Наиболее часто верхние околощитовидные железы обнаруживаются по заднемедиальной поверхности правой и левой долей щитовидной железы (верхняя треть доли), хотя встречаются и на уровне бифуркации общей сонной артерии, за глоткой и пищеводом, и интратиреоидно (1%). Расположение нижних околощитовидных желез более вариабельно: по боковой или задней поверхности, или ниже нижнего полюса щитовидной железы на расстоянии 0,2–1,5 см, в рогах тимуса, в переднем или заднем средостении, интратиреоидно (1–2%). Это объясняется сложным и продолжительным характером миграции зачатка из III–IV жаберного кармана в ходе эмбриогенеза. Топическая диагностика при первичном гиперпаратиреозе опирается на данные УЗИ органов шеи, сцинтиграфии с технетрилом, мультиспиральной компьтерной томографии органов шеи и средостения. При сочетании многоузлового зоба и интратиреоидного расположения околощитовидной железы могут возникнуть дополнительные сложности в верификации различных узлов (узлы щитовидной железы или околощитовидные железы). В настоящей статье обсуждается два клинических случая интратиреоидного расположения околощитовидных желез. Показан алгоритм топического подтверждения диагноза. Определение уровня паратгормона в пунктате из подозрительных образований, которые могут представлять собой интратиреоидные околощитовидные железы или узлы щитовидной железы, поможет избежать диагностических ошибок.

КЛЮЧЕВЫЕ СЛОВА: Первичный гиперпаратиреоз; ПГПТ; пункционная тонкоигольная аспирационная биопсия; ТАБ; интратиреоидная парааденома; паратгормон; ПТГ

ROLE OF PARATHYROID HORMONE MEASUREMENT IN FINE-NEEDLE ASPIRATION BIOPSY WASHOUT IN DIAGNOSIS AND TREATMENT OF PRIMARY HYPERPARATHYROIDISM

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In this article, we discuss difficulties in parathyroid localization modalities in diagnosis of primary hyperparathyroidism. Most often, superior parathyroid glands are located on the posteromedial surface of the right and left lobes of the thyroid gland, however, they also could be found at the carotid bifurcation, behind pharynx and esophagus, as well as inside thyroid gland. Location of the inferior parathyroid glands is more variable: on the side or back surface, or below the lower pole of the thyroid gland, as well as in thymus, posterior or anterior mediastinum, or inside thyroid. Localization modalities of primary hyperparathyroidism are based on neck ultrasonography, scintigraphy with sestamibi, computed tomography of neck and mediastinum. In cases with combination of multinodal goitre and an intrathyroid location of the parathyroid gland, there might be additional difficulties in verification of various patterns (thyroid nodules or parathyroid glands). In this article, we present two clinical cases of intrathyroid location of parathyroid glands. The algorithm of parathyroid adenoma localization is shown. Determination of PTH level in washing liquid after fine-needle aspiration biopsy from necessary punctures of the nodule formations, which can be either intrathyroid parathyroid glands or thyroid nodules, can also help to avoid diagnostic mistakes.

KEYWORDS: Primary hyperparathyroidism; fine needle aspiration biopsy; parathyroid adenoma, parathyroid hormone; PTH

BACKGROUND

Primary hyperparathyroidism – is a condition caused by primary (i.e. not provoked by low calcium level in blood) PTH-hyperproduction which leads to calcium homeostasis disruption. The incidence of PHPT is about 20:100 000 people per year; in recent years there has been a steady increase in incidence due to improved sensitivity and availability of diagnostic methods. The prevalence of PHPT is about 1%, increases with age and reaches 2% and more among patients older than 55 years. For patients older than 60, men to women ratio is 1:3. PHPT is the

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third most common disease after diabetes mellitus and thyroid disorders [1-4].

Overt PHPT is a serious condition because of development of progressive disabling complications such as: disorders of the musculoskeletal system (osteoporosis, hyperparathyroid osteodystrophy , bone deformation, fractures, gait disturbance), renal diseases (nephrolithiasis, nephrocalcinosis, decrease in the filtration and concentration function of the kidneys), gastrointestinal (recurrent defects of the duodenal and stomach mucosa, pancreatitis, calcification of the pancreas, pancreatic calculus) and neurocognitive disorders. Cardiovascular disorders (arterial hypertension, myocardial hypertrophy of the left ventricle and diastolic dysfunction of the left ventricle, rhythm and conduction abnormalities) may also be presented with positive correlation to PHPT level, phosphorus-calcium metabolism disturbance and filtration state of the kidneys [5].

It's now generally accepted, that the preferred therapeutic measure for the vast majority of overt cases of PHPT is parathyroidectomy. The surgical treatment is indicated for all patients with PHPT younger than 50 years, for patients with severe hypercalcemia (the level of total serum calcium is increased on 0.25 mmol / l (1 mg%), according to reference interval established in the laboratory), reduced glomerular filtration rate (less than 60 ml/min/1,73m2), daily calcium excretion more than 400 mg (10 mmol), decreased BMI in radial, femoral bones or vertebrae less than -2.5 SD by the T-score [5,6].

One of the challenging problems of the PHPT diagnostics and surgical treatment is understanding the localization of parathyroid gland lesion before and during operation. In 1986, the famous surgeon John Doppman stated: «The only investigation of the localization, that is indicated for the patient with untreated PHPT – is an experimental vizualization by the surgeon during the operation». In 90-95% of cases, experienced surgeons can determine the localization and remove the adenoma of the parathyroid gland without preoperative instrumental visualization. However, currently the intervention could be carried out only after previous topical diagnosis. Usually there are four parathyroid glands located at the back and on the side of the thyroid gland: two for each lobe. Lungs develop from the endoderm of the third and fourth gill pockets. Differentiation of parathyroid tissue begins when embryo reaches 8-10 mm.

The lower parathyroid glands develop from the dorsal portion of the third gill. The thymus gland develops from the ventral part of the same branchial arch. Their common origin is the cause of the thymic localization of the lower parathyroid glands. In 80-90% of cases the lower parathyroid glands are located at the level of the lower poles of the thyroid gland, but the glands of this pair, as well as additional PTG, can be located in the thickness of the thyroid gland, under its capsule, in the anterior or posterior mediastinum, in the thymus gland, behind esophagus, near the bifurcation of the carotid artery, etc. [8,9]. Such localization may be suspected by ultrasound evaluation. 5-10% adenomas of the parathyroid glands are located atypically due to embryogenesis impairment. It's more common for lower parathyroid glands [7,8].

The most often used instrumental diagnostics methods for PHPT are ultrasound and radionuclide diagnostic methods, such as, planar scintigraphy with 99mTc-sestamibi and single-photon emission computer tomography (SPECT / CT), as well as MSCT with contrast enhancement. According to the literary sources, these methods have different sensitivity and specificity [11, 13].

Ultrasound examination of the neck region is recommended as the first stage of topical diagnosis of PHPT. This diagnostic method is safe and widely used to visualize enlarged parathyroid glands. Sensitivity and specificity of the examination depend on the expert's experience, the size and location of the glands, so the results could be variable. The sensitivity of the method, according to different data, ranges from 36 to 90%, and is correlated with the qualification of the specialist doing the examination. Specificity reaches 99%. According to the results of different authors, with gland mass less than 500 mg, the sensitivity of the method decreases to 30% [5]. Ultrasound examination can identify up to 60-70% of atypically located parathyroid glands. Topical diagnostics is complicated if there is a combination of primary hyperparathyroidism with a multinodular conglomerate goiter. Additional difficulties could occur due to intracapsular location of the PTH, as the adenoma can be squeezed or deformed, which makes it difficult not only to diagnose, but to surgically treat it later. Scintigraphy with technetium (99mTc-MIBI) allows to detect the parathyroid adenomas both on the neck and other regions. The sensitivity of scanning with technetium is 60-90% [11]. Combined with SPECT/CT, this method effectively allows to localize parathyroid adenomas, especially at their dystopic location or after ineffective surgical treatment. However, in the presence of functionally active intrathyroid formations, this method cannot reliably specify their origin. Multispiral computer and magnetic resonance imaging have sensitivity of 90-95%, but low specificity. These studies evaluate the blood flow intensity and clearly model the spatial arrangement. They are also used to localize pathological parathyroid glands, especially in their retrosternal localization. The disadvantages of the method are relatively low availability, high cost and the presence of a significant radiation load [5].

When the clinical diagnosis of PHPT is not in doubt according to clinical and laboratory data, but the topical diagnosis is contraversial, or differential diagnosis with thyroid gland/paratracheal metastasis of a highly differentiated thyroid cancer is required, PTH (and TG in in case of exclusion of metastasis) in the washout fluid from the fine-needle after a aspiration biopsy of suspicious formation could be a useful method. According to the results of foreign authors, its sensitivity and specificity are very high and reach 91% and 100%, respectively [12].

The method is relatively simple to perform. Under the ultrasonic control with a linear sensor of 7.5 MHz 60 mm long, the puncture of modified PTG is performed with a 5.0 or 10.0 ml syringe with a 21-23G needle. Than the lavage with 1.0 ml of stabilized solution is performed through the fine-needle for several times. Afterwards the PTH level is examined in the fluid. In most cases the

PTH level less then 100pg/ml means, that the puncture was performed not from the PTG. The PTH level from the washout fluid, several times higher than the basal level in the blood, indicates the presence of adenoma. [15,16]. The PTH level several times higher than the blood level (usually the result is more than 10 fold higher) can unequivocally prove the presence of an intrathyroid parathyroid adenoma. Previously, the question of the probability of paratyromatosis after multiple parathyroid adenomas fine-needle punctures was discussed in the professional literature, but none of the studies revealed development of parathyromatosis [12]. Among side effects of fine-needle aspiration biopsies different authors highlight local changes (pain, flushing, local inflammation, hemorrhage, etc.) and general effects (syncope, collapse, etc.). During the further surgical treatment no additional complication associated with previous fine-needle puncture could be seen.

Cytological examination of the material obtained with aspiration biopsy of the PTG is quite challenging. Morphologically it's nearly impossible to distinguish separated PTG cells from the follicular tumor cells of the thyroid gland. Considering this circumstance, routine fine-needle puncture biopsy of PTG with further cytological examination in PHPT is not recommended.

To assess the effectiveness of surgical intervention, the intraoperative determination of the PTH level dynamics is performed: the first point - before the operation, the second - 15 minutes after the removal of the adenoma or hyperplastic parathyroid gland [14]. The method is characterized by high predictive value. The decrease in PTH levels on more than 50% indicates successful surgerical outcome.

Sometimes a decrease in PTH level occurs only on the following day, which may be due to additional release of PTH during long-term intraoperative revision and isolation of parathyroid adenoma, or the presence of renal failure [10].

Clinical examples are given as illustrations to the described diagnostic problem.

CASES DESCRIPTION

Clinical case №1

Patient B. 54 years old, admitted to the surgery department of the Endocrinology Research Center with diagnosis: *Primary hyperparathyroidism, skeletal-visceral form. Adenoma of the upper right parathyroid gland. Generalized osteoporosis, with a maximum BMD decrease in lumbar spine up to - 4.2 SD*. Urolithiasis. Bilateral nephrolithiasis. Patient also had previously diagnosed bilateral multinodular euthyroid goiter grade II.

According to previous medical history, increased calcium level in blood was estimated for the first time in February 2017 during routine medical check-up. Later on summer 2017 the diagnosis of PHPT was verified: PTH-137.6 pg / ml (15-65), 25-OH-vitamin D - 27 nmol / l (30-100 nmol / l), total calcium - 2.62 mmol / l (2.10-2.55). According to osteodensitometry, there was a BMD decrease up to -4.2 SD by the T-score in the lumbar spine region, which stands for osteoporosis.

According to the scintigraphy with technetium, the focus of increased accumulation of RFP in the projection of the upper pole of the right lobe was detected (Fig. 1).

Ultrasound examination of the neck organs from June 2017 showed the thyroid gland volume of 13 ml. There were several nodes of 0.4-0.8 cm in the right lobe, one of which was calcinated. In the left lobe there were several zones 0.3 cm in diameter. In the upper third of the right lobe 1.4 cm mass depressed into the tissue of the thyroid gland was defined (intrathyroid parathyroid adenoma?) (Fig. 2). To confirm the diagnosis a fine-needle intrathyroid node biopsy with further PTH level examination in washout fluid was performed with the result of 420 pg/ml.

During the surgical revision a dark brown mass 1.0 cm in diameter was revealed behind the right lobe of the thyroid gland. Afterwards the mass was surgically removed. Several nodes were also palpable in the right lobe 1.0-1.5 cm in diameter. Given the pre-operative data for intrathyroid localization of the PTG, right hemithyroidectomy was performed with the control of the recurrent nerve and normal right lower PTG (0.5 cm). According to the intraoperative ultrasound control – no additional formations in the right lobe of the thyroid gland was determined. Laboratory study of basal PTH level - 201 pg/ml, 20 min after removal – 220 pg / ml. The following day PTH level - 45.54 pg / ml, total calcium level 2.13 mmol / l, ionized calcium 1.05 mmol/l. Absence of a post-surgical decrease in PTH levels can be explained by additional hormone release during long-term revision.

According to histological examination of the postoperative material in the tissue of the right lobe of the thyroid gland with signs of macro- and microfollicular colloid goiter intrathyroidally located adenoma of the parathyroid gland was detected with predominantly solid- trabecular structure of the main cells. Separately located brown tissue was a colloid node.

The patient was discharged from the hospital in a satisfactory condition, the calcium metabolism control once in a month was recommended.

Fig. 1. Scintigraphy of parathyroid glands with technetium. The arrow indicates the area of residual high accumulation of RFP, parathyroid adenoma.

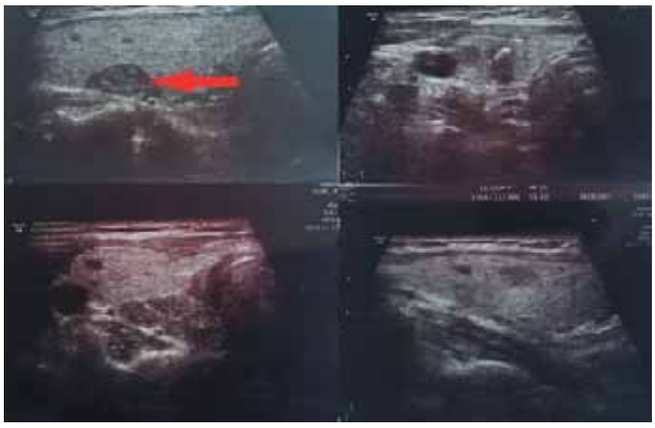

Fig. 2. Ultrasound examination of the thyroid gland. The arrow shows the intrathyroid localization of the parathyroid adenoma surrounded by thyroid tissue. On the right picture - colloidal nodes of the same lobe of the thyroid gland.

Clinical case №2

Patient K. 65 years old, admitted to the surgery department of the Endocrinology Research Center with diagnosis: *Primary hyperparathyroidism, skeletal form. Adenoma of the lower right parathyroid gland. Osteoporosis of the radius with a maximum BMD reduction up to -2.5 SD by T-score. Concomitant diseases: multinodular toxic goiter. Radioiodine therapy from 01.2017 (activity I-131 1.1 GBq). Euthyroidism on the underlying drug therapy*.

From the previous medical history it is known that the total calcium level in blood was maximum increased up to 2.87 mmol / l (2.15-2.55), ionized calcium up to 1.45 mmol / l (1.13-1.32) at the end of 2016.

During further survey in March 2017, an increase in PTH level up to 82.27 pmol / L (1.6-6.9) was detected. The daily calciuria was 12.42 mmol / day (2.5-7.5). Based on the neck ultrasound results, the volume of the thyroid gland - 42 ml, the tissue was changed in chronic autoimmune manner.

In the right lobe a conglomerate node 4 cm in diameter was defined, at the lower pole of the right lobe a hypoechoic mass of 1.4x1.0x0.7 cm was determined (echographic signs of an adenoma of the right lower parathyroid gland) (Fig. 3).

Considering the patient's will to refrain from surgical treatment, Cinacalcet 60 mg / day for two months was prescribed with further decrease of total calcium level to 2.55 mmol / l, and no dynamics in ionized calcium level (1.44 mmol/l). After the unprompted Cinacalcet withdrawal, according to laboratory tests from August 2017 there was an increase in PTH level up to 91.80 (1.6 - 6.9), total calcium level up to 2.81 mmol/l. Scintigraphy with technetium was not carried out, because of a previously defined "hot" node in the thyroid gland according to scintigraphy with iodine 123 (before radioiodine therapy), which would make it difficult to interpret the results of the study (Fig. 4).

On May 2017, patient was diagnosed with osteoporosis (PHPT complication) according to osteodensitometry results of radial bone BMD decrease to -2.5 SD by T-score.

During the surgery the revision of the parathyroid glands without removing of the right lobe of the thyroid gland, was impossible due to the presence of a large conglomerate nodal formation in the right lobe of the

Fig. 3. Ultrasound of the thyroid gland. The blue arrow indicates a colloidal node, the red arrow - intrathyroid parathyroid adenoma.

thyroid gland and the progressive fibrous-adhesive process. Right hemithyroidectomy was performed. In the right lobe of the thyroid gland, two colloid nodes 1,0 and 4,0 cm in diameter were detected. With further revision a hyperplastic upper right PTG 0.7 cm in diameter was revealed. Urgent morphological examination of the removed intrathyroid mass confirmed adenoma. Basal PTH level in blood - 113 pg / ml; 15 min after removal of the mass - 12 pg / ml.

Normalization of total and ionized calcium levels in blood were seen on the following day.

According to routine histological examination, an intrathyroid adenoma of the parathyroid gland with microfollicular structure and attached tissues of parathyroid gland with signs of atrophy were seen. In thyroid gland tissue a picture of multinodular macro-microfollicular colloid goiter with cyst formation and degenerative changes were detected.

DISCUSSION

The management and treatment of patients with PHPT is usually conducted in specialized centers to avoid possible tactical and technical mistakes. Despite of the simplicity of the diagnosis and treatment of this pathology, there are many details, underestimation of which may lead to complications during surgery and need for repeated interventions.

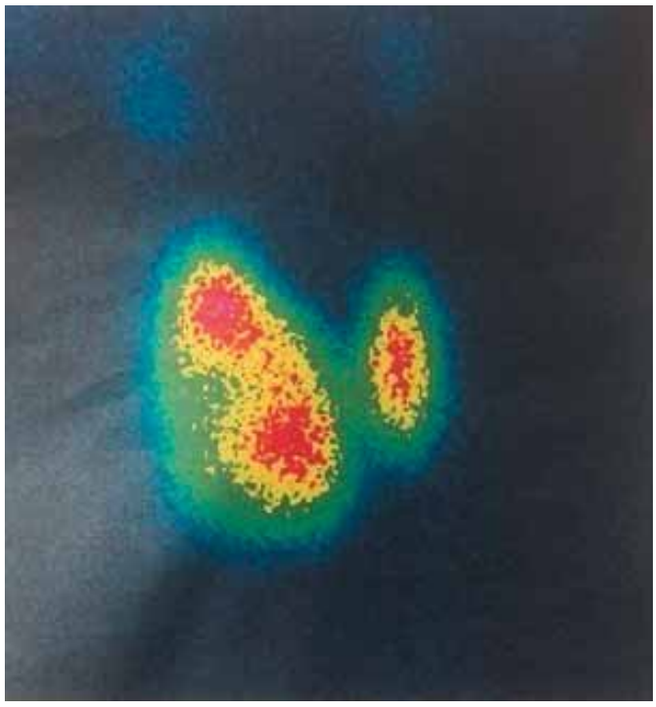

Fig. 4. Scintigraphy of the thyroid gland before radioiodine therapy.

In the first clinical case, there was a risk of removal the colloidal thyroid node abandoning the intrathyroid adenoma, which would result in a second operation. In the second example there were also difficulties with intraoperative verification of the parathyroid adenoma. These problems could be avoided with PTH level determination in the washout fluid from the site of interest on outpatient stage. In some cases, an intraoperative ultrasound control is needed. Usually it is performed in case of discrepancy between preoperative topical diagnostics results and the picture seen during surgery. This proves the importance of accurate topical verification of the adenoma during preoperative stage.

CONCLUSION

Precise topical diagnosis of the parathyroid adenoma is necessary for the successful surgical treatment of PGPT. The first step after confirming the clinical diagnosis of primary hyperparathyroidism is an ultrasound examination of the neck region performed by the expert. In case of an absence of clear visualization or small size of the formation, it is recommended to perform a scintigraphy with technetium or MSCT of the neck and mediastinum with contrast reinforcement.

One of the effective methods of topical diagnosis of PHPT is the determination of PTH level in fine-needle washout fluid after aspiration biopsy. This method showed high sensitivity (91%) and specificity (100%). The examination of PTH level in washout fluid from the fine-needle is not a routine method of diagnosis and is recommended only in case of verified PHPT for a differential topical diagnosis between parathyroid tissue and other formations: a tissue of the thyroid gland in the case of concomitant multinodal goiter, paratracheal lymph nodes, thyroid cancer metastasis, and also for confirmation or exclusion of intrathyroid parathyroid adenomas.

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