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Parathyroid hormone in washout fluid seems to be superior to cytology for localization of the lesion in MIBI-negative patients with primary hyperparathyroidism

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Background/aim: Primary hyperparathyroidism (PHPT) is characterized by increased calcium (Ca) and parathyroid hormone (PTH) levels. Surgical removal of the culprit hyperfunctioning parathyroid gland is the preferred treatment. In this study, we aimed to determine whether PTH-washout or cytological examination of suspicious lesions was superior in MIBI-negative patients diagnosed with PHPT.

Materials and methods: We retrospectively evaluated the medical records of 98 patients diagnosed with PHPT. Seventy-six patients who had positive parathyroid scintigraphy and who did not undergo parathyroidectomy in our center due to various reasons were excluded. We evaluated the remaining 22 patients with negative scintigraphy. Medical records including PTH levels in serum and washout fluid of fine-needle aspiration biopsy (FNAB), biochemical data, cytological results of FNAB, and histologic reports were reviewed.

Results: The patients had a mean age of 50 ± 9 (31–72) years, serum Ca of 10.9 ± 0.5 (10.3–12.7) mg/dL, serum PTH of 285 ± 156 (107.2–679) pg/mL, and PTH of washout fluid of 19,523 ± 38,632 (1410–166,000) pg/mL. Cytological evaluation revealed insufficient material in 9 patients and cells of indeterminate origin in 4 patients.

Conclusion: Our results showed that when evaluating ambiguous lesions on neck ultrasound, measuring the PTH level in washout fluid of FNAB is a reliable and effective method for diagnosis of parathyroid lesions and is superior to FNAB for localization.

Key words: Hyperparathyroidism, parathyroid hormone washout, fine needle aspiration cytology, parathyroidectomy

1. Introduction

Primary hyperparathyroidism (PHPT), which is characterized by increased serum calcium (Ca) and parathyroid hormone (PTH) levels, is caused by solitary or multiple hyperfunctioning parathyroid lesions (adenoma, hyperplasia, and rarely cancer). The most common etiology is solitary adenoma in 85% of cases. The preferred treatment modality is removal of the culprit hyperfunctioning parathyroid lesion. Until recently, bilateral neck exploration has been the standard surgical approach. Today, if preoperative localization of the hyperfunctioning gland and rapid intraoperative PTH measurement is accessible, minimal invasive parathyroidectomy (MIP) is the preferred approach (1). The success of surgery does not solely depend on the experience of the surgeon, but also on preoperative localization of the hyperfunctioning parathyroid lesion (2,3).

Ultrasonography (USG) and 99m technetium-methoxyisobutylisonitrile (99mTc-MIBI) scintigraphy are widely used imaging modalities for detecting the hyperfunctioning parathyroid lesion, while computed tomography (CT)/magnetic resonance imaging (MRI) or single-photon emission computed tomography (SPECT) are the less preferred ones. However, diagnostic imaging studies may yield false-positive (other cervical pathologies and nodular goiter) or false-negative (lesions small in size or having low activity) results (4).

PTH measurement in washout fluid of fine-needle aspiration biopsy (FNAB) was first defined by Doppman et al. in 1983. PTH-washout and FNAB are effective methods for detecting parathyroid lesions (5). A fast and accurate diagnosis of parathyroid origin of the cervical lesions is possible. PTH measurement in washout fluid of FNAB of 99mTc-MIBI-negative lesions that cannot be clearly identified on USG is especially helpful in localization of a hyperfunctioning parathyroid gland.

In this study, we aimed to determine whether PTH-washout or cytological examination of suspicious lesions

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was superior in MIBI-negative patients diagnosed with PHPT by means of retrospective analysis of electronic data.

2. Materials and methods

2.1. Patients

Electronic medical records collected from January 2011 to July 2016 were scanned for the ICD code (E21.0) identifying PHPT. Patients who underwent parathyroidectomy according to the 4th International Workshop of 2014 were evaluated (6). Those with preoperative positive localization imaging (MIBI and/or USG) and those who did not undergo parathyroidectomy in our center due to various reasons (lack of approval from the patient, high surgical risk, or admission to another health facility) were excluded. Those who underwent MIP and had a pathological diagnosis of parathyroid adenoma or cancer were evaluated after a preoperative FNAB study for localization.

Electronic records regarding demographic data, clinical features, and laboratory data of the patients meeting the abovementioned criteria were evaluated. Cytological results of FNAB and histological evaluation of the surgical specimens were evaluated. The informed consent of the patients was obtained.

2.2. Neck USG, FNAB, and PTH measurements

Doppler USG of the neck with 5–10-MHz linear array transducers (Mindray DC-T6 Diagnostic Ultrasound System, Shenzhen, China) was performed by two experienced endocrinologists. USG-guided biopsies were performed using sterile 22-gauge needles and 10-mL syringes. Biopsy samples were smeared on glass slides for cytologic examination. Immediately after aspiration biopsy, the needles were rinsed with 1 mL of normal saline solution and PTH was measured in the washout fluid. The washout samples with a PTH level above 3000 pg/mL were studied again after 1/10–100 dilution. PTH in serum and in FNAB fluid samples was measured with the Abbott Architect i2000 immunoassay analyzer (Abbott Diagnostics, Lake Forest, IL, USA) by chemiluminescent microparticle immunoassay method. The detection range was between 3 and 3000 pg/mL and the reference range was 15–68.3 pg/mL.

2.3. Statistical analysis

Statistical analysis was done using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Age, serum Ca, serum PTH, and PTH-washout levels are given as mean ± SD. The results of cytological examinations are defined as frequencies.

3. Results

From the electronic database of the endocrinology unit, 98 patients who were diagnosed with PHPT and eligible for surgery were selected. Among them, 58 patients who had positive imaging (99mTc-MIBI scan and/or USG) and 18 patients who did not undergo surgery in our center were excluded.

FNAB and PTH-washout were performed for the remaining 22 patients with negative 99mTc-MIBI results and ambiguous images on neck USG. All patients were female. The mean age was 50 ± 9 (31–65) years, serum Ca level was 10.9 ± 0.5 (10.3–12.7) mg/dL, and serum PTH level was 285 ± 156 (107.2–679) pg/mL. Mean PTH-washout level was 19,523 ± 38,632 (1410–166,000) pg/mL. Cytologic results were as follows: 9 insufficient materials (41%), 8 benign parathyroid cells (36%), 4 cells of indeterminate origin (18%), and 1 suspicious for malignancy (5%). Histopathological examination of surgical specimens revealed benign parathyroid adenoma in 21 patients and parathyroid carcinoma in one patient. Details of clinical features and laboratory data are shown in the Table.

4. Discussion

In this study, we showed that PTH-washout is an easy and helpful method. It is superior to cytological examination in preoperative localization of hyperfunctioning parathyroid lesions in patients with negative imaging results (USG and MIBI).

MIP has some benefits (shortened length of operation and in-hospital stay, improved surgical success, smaller incision, less postoperative pain, and quicker healing) over standard bilateral neck exploration surgery for treatment of PHPT (7,8). Before MIP, it is of utmost importance to detect the exact localization of the hyperfunctioning parathyroid lesion. Frequently used imaging modalities including USG, 99mTc-MIBI scintigraphy, SPECT, CT, or MRI achieve success in most cases. However, there are some challenging cases that are invisible on imaging.

USG is an easily feasible, widely available, cheap, and noninvasive imaging modality. The sensitivity of USG for detecting parathyroid lesions is 72%–85% (9–11). However, it is operator-dependent and success is closely related to expertise. Furthermore, parathyroid lesions can be confused and misdiagnosed with thyroid pathologies, vascular structures, lateral cervical lymph nodes, or the esophagus (12).

99mTc-MIBI scintigraphy is another widely used imaging modality for preoperative localization of parathyroid lesions. It is more successful in detecting solitary or ectopic adenomas than multiple adenomas. Despite its high sensitivity (71%–93%) and high specificity (90%), the small size of parathyroid adenomas, oxyphilic cell content, degree of apoptosis, or necrosis may lessen MIBI uptake and lead to false negative results (13–15). Hypermetabolic thyroid lesions such as toxic thyroid

Table. Clinical features and laboratory data of patients with PHPT undergoing FNAB with PTH-washout.

Patient	Age	Sex	Preop Ca* (mg/dL)	Preop PTH** (pg/mL)	PTH-washout (pg/mL)	Postop Ca (mg/dL)	Postop PTH (pg/mL)	Cytology	Surgical result
1	51	F	12.7	540	36,200	9.8	9.9	SFM	PA
2	56	F	10.3	164.5	8900	8.8	32	BPC	PA
3	49	F	10.9	140	4600	8.9	26.4	ND	PA
4	52	F	10.6	347	9480	8.7	34.8	BPC	PA
5	55	F	11	292	45,500	9.8	14.2	ND	PA
6	46	F	11.2	547.2	90,500	8.8	30.1	ND	PA
7	55	F	11.6	339.5	3870	8.6	60.4	ND	PA
8	54	F	10.7	146	4070	8.6	44	ND	PA
9	50	F	10.9	679	2616	9.0	24.8	ND	PC
10	31	F	11.5	329.9	2020	7.9	20.9	BPC	PA
11	53	F	10.5	492	1410	8.2	18.7	IDC	PA
12	35	F	10.7	234	7860	8.5	33	BPC	PA
13	51	F	10.3	107.2	5500	8.9	28	ND	PA
14	48	F	10.9	279	166,000	9.3	56	BPC	PA
15	65	F	11.2	117	6914	8.1	36.4	BPC	PA
16	50	F	10.5	150.5	2812	8.3	36	IDC	PA
17	72	F	11.2	240.2	9320	8.6	57	IDC	PA
18	33	F	10.4	212	2080	9.5	56	IDC	PA
19	47	F	10.8	304.4	5100	8.7	42	ND	PA
20	55	F	11.1	218.9	9100	8.6	35	BPC	PA
21	54	F	10.9	135	3800	8.8	48	ND	PA
22	49	F	11.2	256	1856	8.9	51	BPC	PA

BPC: Benign parathyroid cells; Ca: calcium; IDC: indeterminate cells; ND: nondiagnostic; PTH: parathyroid hormone; PA: parathyroid adenoma; PC: parathyroid carcinoma; SFM: suspicious for malignancy.
*Ca normal reference range: 8.4–10.2 mg/dL; **serum PTH normal reference range: 15.0–68.3 pg/mL.

adenomas and oncocytic tumors may retain MIBI and yield false positive results (16).

FNAB and PTH-washout are additional methods for differentiating parathyroid lesions from other suspicious lesions detected by imaging modalities and localizing parathyroid lesions. The efficacy and validity of these methods have been shown in recent studies (17–19). However, no consensus has been reached on PTH-washout cut-off values for parathyroid tissue.

A slightly higher PTH level in washout fluid than in serum is sufficient for parathyroid localization in the case of remeasurement after dilution (17). Various cut-off values have been proposed in different studies. Maser et al. proposed that a PTH level above the normal reference laboratory range was sufficient for diagnosis (18), while Abdelghani et al. proposed that the PTH level in washout fluid should be higher than the serum level (20). When small volumes (0.5 or 1 mL) of saline usage for rinsing of the aspirates are taken into account, it can be assumed that the level would be at least 10–20 times lower than the exact value (21). However, in most of the studies PTH levels of washout were hundreds and thousands of times greater than serum PTH levels (3,19,22). Similar to the literature, we demonstrated PTH-washout levels hundreds of times higher than in serum.

FNAB of the parathyroid gland was another variable in our study. It is quite difficult to differentiate abnormal thyroid tissue from parathyroid tissue and there are no absolute criteria for discrimination. In previous studies, usage of a combination of cytomorphological features or immunohistochemistry stains were advised (23–25). Although FNAB is an easily feasible method worldwide for the diagnosis of parathyroid lesions, its usefulness is limited due to low sensitivity, smear inadequacy, and contamination with thyroid tissue (26,27). In more than half of the cases (13 patients) cytologic evaluation was nondiagnostic, with insufficient material or cells of indeterminate origin. A high PTH level in washout fluid of FNAB despite nondiagnostic cytology may indicate that a small number of cells is insufficient to make an accurate diagnosis. In addition, postoperative histologic confirmation of parathyroid lesions proves that PTH-washout of FNAB of suspicious lesions is 100% successful for preoperative localization compared to 36% with FNAB and that PTH-washout is superior to cytologic evaluation.

Although hemorrhage, hematoma, and dysphonia may complicate FNAB and PTH-washout procedures, our patients tolerated them well and no complications occurred.

Our study has some limitations. First, the number of patients was limited. Second, we presented the data of patients with high PTH levels of FNAB washout retrospectively and compared concordance with parathyroidectomy results. Obviously, there are some other cervical lesions that may be confused with parathyroid glands and PTH-washout of FNAB of these lesions would probably be low. On the other hand, whether the putative lesion detected by ultrasound is of parathyroid origin can only be ascertained after histologic evaluation after surgery. In our study, we only included patients who underwent parathyroidectomy after PTH-washout of FNAB fluid. PTH-washout-negative patients did not undergo surgery and were not included. As a result, the efficacy of PTH-washout can only be proven after studies are done on larger numbers of both PTH-washout-positive and -negative patients.

In conclusion, we showed that PTH-washout of FNAB of hyperfunctioning parathyroid glands is an important method for localization. FNAB along with PTH-washout may serve as a suitable diagnostic method in challenging cases with ambiguous US features and negative 99mTc-MIBI scintigraphy studies. In addition, PTH-washout of FNAB fluid is superior to cytologic evaluation of FNAB for the diagnosis of parathyroid lesions.

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