

Value of preoperative ultrasound-guided fine-needle aspiration for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients

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Abstract

To evaluate the value of preoperative ultrasound-guided fine-needle aspiration (UG-FNA) of ultrasound-detected suspicious parathyroid nodules for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients.

From May 2008 to December 2016, Tc-99m MIBI-negative primary hyperparathyroidism patients with ultrasound-detected suspicious cervical nodules underwent UG-FNA. The sample obtained from the solid component of the nodule was subjected to cytological evaluation and immunohistochemical staining. The sample obtained from the cystic component of the nodule or solid nodules was subjected to parathyroid hormone determination. After aspiration, the nodules underwent surgical resection or follow-up.

Fifteen nodules (5 cystic, 5 cystic and solid, and 5 solid) from 15 patients were subjected to UG-FNA. Aspirate samples were obtained from 12 of the nodules, and the parathyroid hormone (PTH) levels of these samples were markedly elevated (range: 302–>2500 pg/mL). The samples obtained from the solid components of the 4 cystic and solid and 4 solid nodules were subjected to cytological evaluation, and parathyroid cells were identified in 5 of them. Of these 5 cases, 4 were subjected to immunohistochemical staining, which revealed PTH positivity in the cell block. The UG-FNA results suggested that the suspicious nodules were all parathyroid lesions. The surgical pathology results of 13 cases confirmed the UG-FNA results; the follow-up of 2 cases did not reveal any significant change.

The cytological evaluation, immunohistochemical staining, and aspirate fluid PTH determination of UG-FNA were helpful for preoperative localization in Tc-99m MIBI-negative primary hyperparathyroidism patients with ultrasound-detected suspicious parathyroid nodules and can be applied selectively or in combination. Aspirate sample PTH determination should be preferred for nodules with cystic components. Further prospective study with large population is needed to confirm our conclusions.

Abbreviations: MIBI = sestamibi, PHPT = primary hyperparathyroidism, PTH = parathyroid hormone, UG-FNA = ultrasound-guided fine-needle aspiration, US = ultrasound.

Keywords: fine-needle aspiration, parathyroid adenoma, parathyroid hormone, Tc-99m MIBI, ultrasound

1. Introduction

Primary hyperparathyroidism (PHPT) is caused by adenomatous and hyperplastic glands or adenocarcinomas that hypersecrete

parathyroid hormone (PTH), and its treatment requires surgical resection of the abnormal glands. Most surgeons prefer to use localization studies before performing the primary parathyroidectomy because preoperative localization may reduce the duration of the surgery, decrease complication rates, and reduce the incidence of persistent or recurrent PHPT.^[1] Dual-phase Tc-99m MIBI scans are commonly used in parathyroid lesion preoperative localization studies, but the sensitivity of these scans depends on the weight of the lesions and oxyphil cell content;^[2–4] therefore, false-negative results can occur when the lesion is small or the solid components is smaller. Ultrasound (US) is also commonly used in parathyroid lesion preoperative localization studies and is more sensitive than the Tc-99m MIBI scan.^[3,5] US can detect lesions that are small or in which the solid component is small; however, it is sometimes difficult to distinguish between a parathyroid lesion and a thyroid nodule or a lymph node. Ultrasound-guided fine-needle aspiration (UG-FNA) is a minimally invasive technique that can determine whether the suspicious nodule is a parathyroid lesion by cytological evaluation, immunohistochemical staining, and aspirate fluid PTH determination.^[6,7] The aim of this study was to evaluate the value of preoperative UG-FNA for the localization of US-detected suspicious parathyroid nodules in Tc-99m MIBI-negative PHPT patients.

Editor: Gaurav Malhotra.

This work was supported by the National Natural Science Foundation of China (81171354).

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:49(e9051)

Received: 9 February 2017 / Received in final form: 27 September 2017 /

Accepted: 13 November 2017

<http://dx.doi.org/10.1097/MD.0000000000009051>

2. Materials and methods

2.1. Study design

The local institutional review board approved this study (Peking Union Medical College Hospital, China). All patients provided their informed consent before undergoing UG-FNA. From May 2008 to December 2016, all PHPT patients referred to this institution underwent a Tc-99m MIBI scan and cervical US examination. The patients, whose Tc-99m MIBI was negative but had US-detected suspicious parathyroid nodules, underwent UG-FNA. The samples obtained from the solid component of the nodules were subjected to cytological evaluation and immunohistochemical staining. The samples obtained from the cystic component of the nodules were subjected to parathyroid hormone determination. After the aspiration, the nodules underwent surgical resection or long-term serum or radiological follow-up.

2.2. Tc-99m sestamibi (MIBI) parathyroid scintigraphy

After intravenous injection of Tc-99m MIBI, planar images of the head and neck region and chest were performed at a matrix size of 256×256 (300k counts per frame) with a pinhole collimator. Scintigraphy was performed as a dual-phase single tracer examination. Images were acquired with the patient in the supine position for 15 to 25 minutes and 1.5–2 hours after injection of the radiopharmaceutical.

2.3. Cervical ultrasound (US) examination

All cervical US examinations were performed by 2 experienced radiologists (one with 25 years and one with 10 years of cervical US examination experience) using a linear probe (L12-5 IU22; Philips Medical System Ultrasound, Bothell, WA). The patients were in the supine position with a pillow beneath their shoulders to slightly hyperextend the neck. The usual localizations of the parathyroid glands were scanned to detect any lesions suggestive of a parathyroid pathology. A detailed examination of all localizations and of the upper mediastinum entry was completed until the end, regardless of whether a lesion was detected during the procedure. The thyroid gland was also evaluated by US, and the size of the thyroid lobes and characteristics of the thyroid parenchyma and nodules were noted.

2.4. UG-FNA

All UG-FNA procedures were performed by 1 experienced radiologist (20 years of UG-FNA experience) using a linear probe (L12-5 IU22; Philips Medical System Ultrasound, Bothell, WA) monitoring the direction and position of the needle. The patients were in the supine position with a pillow beneath their shoulders to slightly hyperextend the neck. The neck of the patients was disinfected and covered with a sterile towel. After the administration of 2% lidocaine local anesthesia, a 21-G needle connected to a 10-mL syringe penetrated the nodules. The needle aspirated several times in different parts of the nodule by maintaining negative pressure. After obtaining a sufficient amount of sample, the negative pressure was eliminated and the needle was removed. The samples obtained from the solid components were immediately smeared onto 3 to 5 sheets and fixed with 95% ethanol, while the remaining cell blocks were fixed with 10% formaldehyde. The samples obtained from the cystic components were injected into EDTA-coated tubes.

2.5. Assessment of aspirate samples

After hematoxylin and eosin staining, the smears underwent cytological evaluation. The cell blocks underwent immunohistochemical staining, including the PTH stain. Aspirate fluid PTH determination was performed using the Intact PTH Assay Kit (IMMULITE/IMMULITE 1000 Intact PTH, Siemens Medical Solutions Diagnostics, Los Angeles, CA).

3. Results

From May 2008 to December 2016, the Tc-99m MIBI scans of 15 PHPT patients (8 males and 7 females, mean age: 48.9 ± 16.5 years, age range: 22–75 years; preoperative serum PTH: 63.7 pg/mL to more than 2500 pg/mL, reference range: 7–53 pg/mL) were negative, but cervical US detected one suspicious nodule in each patient (Table 1). Thirteen patients were referred for hypercalcemia and 2 patients were referred for suspected thyroid enlargement. The maximum dimension of the 15 nodules on US was 3.9 ± 1.5 cm (range: 1.1–6.4 cm). Eight nodules were located behind the thyroid or close to the lower pole of the thyroid. One nodule was located behind the upper part of the right lobe of the thyroid. Four nodules were located inside the thyroids, 1 nodule was located behind the thyroid with some parts protruding into the thyroid, and 1 nodule was located in the suprasternal fossa (lateral to the right subclavian artery). Five nodules were cystic (Fig. 1), 5 were cystic and solid (Fig. 2), and 5 were solid (Fig. 3). Ten cases (case nos. 2, 4, 5, 6, 8–10 and 13–15) received computerized tomography scans. Suspicious nodules were also detected in the locations where US detected them, but it could not be determined whether they were parathyroid lesions.

All 15 suspicious nodules underwent UG-FNA. Aspirate fluid was obtained from 10 nodules with a cystic component. Two samples were obtained from the solid nodule, and the PTH levels of 12 cases were markedly elevated (the PTH level was 302 and 337 pg/mL in 2 cases and >2500 pg/mL in the other 10 cases). Samples were obtained from the solid components of the 4 cystic and solid nodules and 4 solid nodules. The samples obtained from the solid components were subjected to cytological evaluation, and parathyroid cells were identified in 5 of them (Fig. 4). Four cases were subjected to immunohistochemical staining and revealed PTH positive in the remaining cell block (Fig. 5). The UG-FNA results suggested that all of the suspicious nodules were parathyroid lesions.

Thirteen patients with hypercalcemia underwent surgical resection, and the pathologies included 11 parathyroid adenomas, 1 parathyroid hyperplasia and 1 parathyroid carcinoma. Particularly, the histopathology of 11 parathyroid adenomas was independently reviewed. Of them, 9 (81.8%) cases were chief cell predominant (Fig. 6). The remaining 2 cases (18.2%) were oxyphil cell predominant (Fig. 7). Two asymptomatic cases had been followed-up by serum PTH determination and US examination, 1 case for 5 years and the other case for 7 years; no significant change was found in these 2 cases.

4. Discussion

Large epidemiological studies have suggested that in 85% of PHPT patients, the disease is caused by a solitary parathyroid adenoma that secretes PTH, while in the other 15% of patients, it is caused by multiple-gland hyperplasia, multiple adenomas, or polyclonal hyperfunction. Furthermore, in less than 1% of PHPT patients, it is caused by carcinoma or a functional cyst.^[8,9] The distribution of this study population was generally consistent

Table 1

Clinical and ultrasound features of the 15 PHPT cases and the corresponding pathology results.

Case	Age/ Sex	PTH-s, pg/mL	Location	US finding	UG-FNA			Surgical histology/ Follow-up
					Cytology	Immunohisto- chemistry	PTH-a (pg/ml)	
1	23/M	81.4	Below the lower pole of the left lobe of the thyroid	Cystic nodule	NA	NA	302	Followed-up for 5 years with no significant change found
2	75/F	568	In the right lobe of the thyroid	Cystic nodule	NA	NA	>2500	PTA with cystic change, chief cell predominant
3	68/M	802	Behind the lower pole of the right lobe of the thyroid	Cystic nodule	NA	NA	>2500	PTA with cystic change, chief cell predominant
4	54/F	193	Behind the lower pole of the right lobe of the thyroid	Cystic nodule	NA	NA	>2500	PTA with cystic change, chief cell predominant
5	66/M	427	In the lower part of the left lobe of the thyroid	Cystic nodule	NA	NA	>2500	PTA with cystic change, oxyphil cell predominant
6	52/F	317	In the suprasternal fossa (lateral to the right subclavian artery)	Cystic and solid nodule	NA	NA	>2500	PTA with cystic change, chief cell predominant
7	64/M	444	Behind the left lobe of the thyroid	Cystic and solid nodule	Negative	NA	>2500	PTA with cystic change, chief cell predominant
8	22/F	382	Behind the lower part of the left lobe of the thyroid	Cystic and solid nodule	Favors PT tissue	NA	>2500	PTA with cystic change, chief cell predominant
9	37/M	562	In the lower part of the left lobe of the thyroid	Cystic and solid nodule	Favors PT tissue	PTH (+)	>2500	PTA with cystic change, chief cell predominant
10	43/F	390	In the lower part of the right lobe of the thyroid	Cystic and solid nodule	Negative	NA	>2500	PTA with cystic change, chief cell predominant
11	50/M	172	Behind the middle part of the right lobe of the thyroid with some parts protruding into the thyroid	Solid nodule with hypoechogenicity	Favors PTA	PTH (+)	NA	PTA, oxyphil cell predominant
12	58/F	>2500	Behind the upper part of the right lobe of the thyroid	Solid nodule with uneven hypoechogenicity	Favors PT tissue	PTH (+)	NA	Parathyroid hyperplasia
13	26/F	63.7	Behind the lower pole of the left lobe of the thyroid	Solid nodule with uneven hypoechogenicity	Favors PT tissue	PTH (+)	NA	Followed-up for 7 years with no significant change found
14	51/M	1140	Below the lower pole of the right lobe of the thyroid	Solid nodule with uneven hypoechogenicity	Negative	NA	>2500	PTC
15	44/M	95.2	Behind the lower pole of the left lobe of the thyroid	Solid nodule with isoechochogenicity	NA	NA	337	PTA, chief cell predominant

NA=not available, PHPT=primary hyperparathyroidism, PT=parathyroid, PTA=parathyroid adenoma, PTC=parathyroid carcinoma, PTH-a=intact parathyroid hormone level-aspirate fluid, PTH-s=intact parathyroid hormone level-serum (reference range: 7–53 pg/mL), UG-FNA=ultrasound-guided fine-needle aspiration, US=ultrasound.

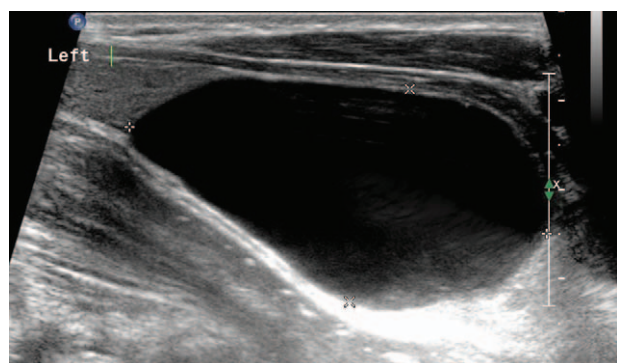


Figure 1. A 23-year-old male was referred for suspected thyroid enlargement. The serum PTH level of the patient was 81.4 pg/mL and Tc-99m MIBI was negative, but US found a cystic nodule behind the lower pole of the left lobe of the thyroid. The aspirate fluid PTH level of the patient was 302 pg/mL. The patient was followed-up with serum PTH determination and US examination for 5 years; no significant change was found. MIBI = sestamibi, PTH=intact parathyroid hormone, US=ultrasound.

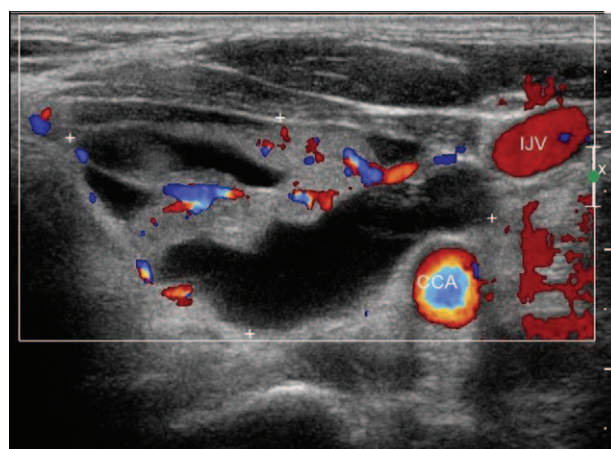


Figure 2. A 37-year-old male was referred for hypercalcemia. The serum PTH level of the patient was 562 pg/mL and Tc-99m MIBI was negative, but US found a cystic and solid nodule in the lower part of the left lobe of the thyroid. The cytological evaluation suggested parathyroid tissue and the PTH stain was positive. The aspirate fluid PTH level of the patient was >2500 pg/mL. Surgical histology confirmed PTA with cystic change. CCA=common carotid artery, IJV=internal jugular vein, MIBI = sestamibi, PTH=intact parathyroid hormone, US=ultrasound.

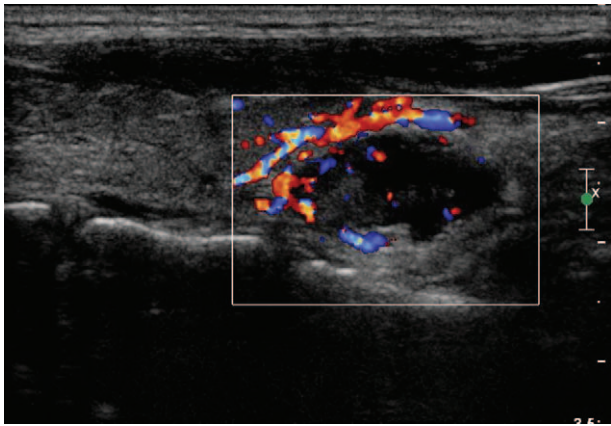


Figure 3. A 26-year-old female was referred for suspected thyroid enlargement. The serum PTH level of the patient was 63.7 pg/mL and Tc-99m MIBI was negative, but US found a solid nodule with uneven echogenicity behind the lower pole of the left lobe of the thyroid. The cytological evaluation suggested parathyroid tissue and the PTH stain was positive. The patient was followed-up with serum PTH determination and US examination for 7 years; no significant change was found. MIBI = sestamibi, PTH=intact parathyroid hormone, US=ultrasound.

with that distribution. In the 13 cases in which surgical pathology was obtained, 11 cases (84.6%, 11/13) were confirmed as solitary parathyroid adenoma, 1 case (7.7%, 1/13) was confirmed as parathyroid hyperplasia and 1 case (7.7%, 1/13) was confirmed as parathyroid carcinoma. This study included Tc-99m MIBI-negative but US-detected suspicious cervical nodules, and Tc-99m MIBI negativity was dependent on the weight of the parathyroid lesion, location, and oxyphil cell content;^[2-4] therefore, these lesions were atypical in location and US characteristics. The location atypicality was in the thyroid (in 4 cases) and lateral to the right subclavian artery (in 1 case), and 1 case had some parts protruding into the thyroid. The US characteristic atypicality was anechogenicity (in 10 cases), uneven hypoechogenicity (in 3 cases), and isoechogenicity (in 1 case). Therefore, it was difficult to accurately diagnose these Tc-99m MIBI-negative nodules using only US. Based on the

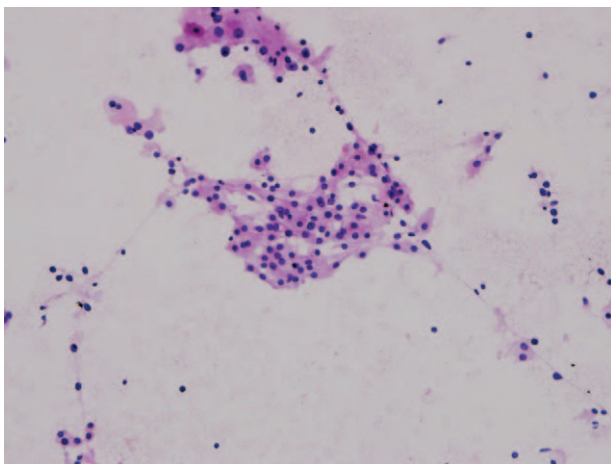


Figure 4. In smears, parathyroid cells are distinctly smaller, monotonous, and generally show neuroendocrine-type features. Some have variable amounts of an oncocyte or a clear cytoplasm. Colloid is absent (hematoxylin and eosin stain, 300 \times).

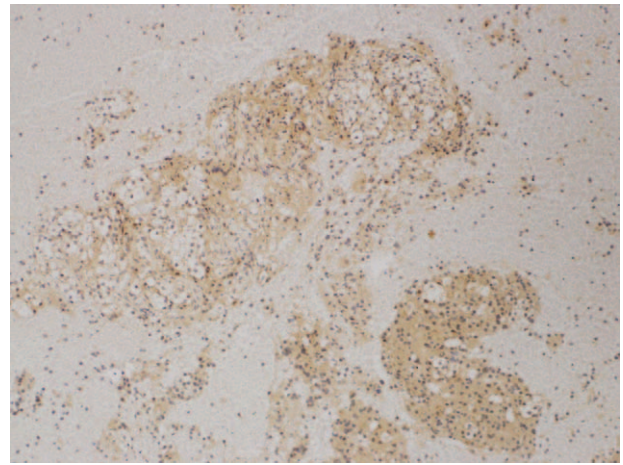


Figure 5. Immunohistochemical stain for parathyroid hormone is positive (150 \times).

histopathology, 9 (81.8%) of the 11 parathyroid adenomas were chief cell predominant. Only 2 (18.2%) cases were oxyphil cell predominant, which may partially account for the negative results of the MIBI scan.

Several studies have demonstrated that cytological evaluation, immunohistochemical staining and aspirate fluid or rinse PTH determination of UG-FNA were helpful for preoperative localization in PHPT patients. Abraham et al^[6] found that the sensitivity of cytological evaluation was 91% with a specificity of 95%. Owens et al^[7] found that the nodules that were markedly elevated in rinse PTH determination were all parathyroid lesions. Kwak et al^[10] found that the sensitivity of the rinse PTH was 92.9% with a specificity of 100%. Erbil et al^[11] found that the sensitivity and positive predictive value of PTH-FNA to localize parathyroid adenoma were both 100%. Lieu^[12] suggested that the immunohistochemical staining of cell blocks could correct the incorrect result obtained by cytological evaluation. In our study, according to the quantity of the samples, all cases underwent at least immunohistochemical staining or aspirate sample PTH determination; therefore accurate preoperative localizations were

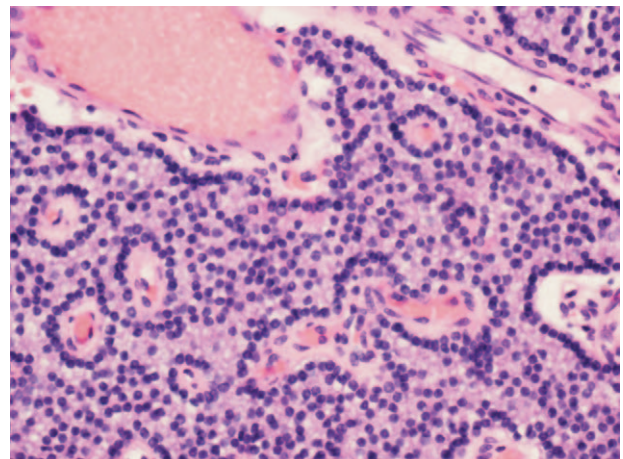


Figure 6. Histopathological demonstration of chief cell predominant parathyroid adenoma (hematoxylin and eosin stain, 200 \times).

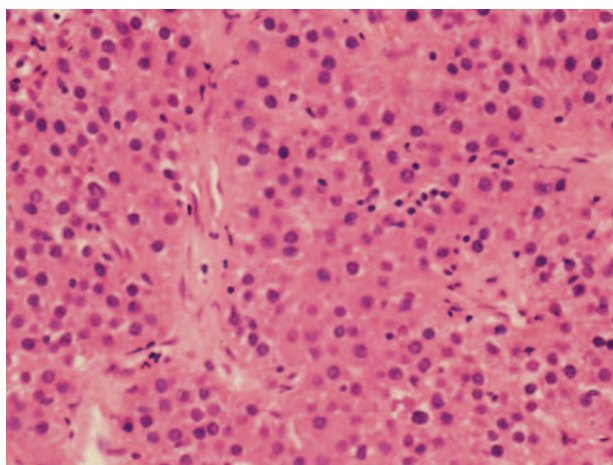


Figure 7. Histopathological demonstration of oxyphil cell predominant parathyroid adenoma (hematoxylin and eosin stain, 200 \times).

obtained. For nodules containing solid components, cytological evaluation may provide a negative result; therefore, the samples should be obtained from different parts of the nodule to reflect the cytology of the different parts, and a sufficient amount of sample should be obtained to perform immunohistochemical staining. For nodules containing cystic components, because a sufficient amount of fluid could easily be aspirated at one time, aspirate fluid PTH determination is the preferred method. It is worth mentioning this because several studies have suggested that rinse PTH determination was useful for a parathyroid pathology diagnosis.^[7,10] In our study, 2 samples from the solid nodules also underwent rinse PTH detection and were verified as parathyroid lesions. Samples obtained from the solid components may be combined with rinse PTH determination in future studies.

In this study, aspirate fluid PTH determination had no reference value, but Abraham et al^[6] reported an aspirate fluid PTH value of the thyroid nodule of 9.0 ± 1.0 pg/mL, while Erbil et al^[11] reported an aspirate fluid PTH value of the thyroid nodule of 48 ± 7 pg/mL (range: 5–57 pg/mL). The lowest aspirate fluid PTH value in this study (302 pg/mL) is markedly higher than those reported in the literature; therefore, the interpretation of the aspirate fluid PTH value was not affected. In addition, in the 12 cases in which an aspirate sample PTH value was obtained, the serum PTH values (81.4 and 95.2 pg/mL) of the 2 cases that had the lowest aspirate fluid PTH values (302 and 337 pg/mL) were significantly lower than those of the other 10 cases (317–1140 pg/mL) in which the aspirate fluid PTH values were greater than the limit of quantification (2500 pg/mL), suggesting that the aspirate fluid PTH value is related to the serum PTH value. However, further studies with larger sample sizes are needed to validate these findings.

In our study, the serum PTH values of 2 cases (81.4 pg/mL in one case and 63.7 pg/mL in the other case) were slightly higher than the upper limit of the reference range (7–53 pg/mL) and these 2 patients were referred to this institution only for suspected thyroid enlargement. After determining parathyroid lesions by UG-FNA, the 2 patients selected follow-up instead of surgical

resection because they had no other symptoms. These 2 cases show that UG-FNA can determine lesions that lead to elevated PTH levels in asymptomatic PHPT patients. Therefore, the changes in lesion size and structure by US, in addition to the change in serum PTH, should be monitored in these patients.

Our study has limitations. PHPT is a common endocrine disease with an estimated prevalence is 0.1–0.2%.^[8] However, our study included Tc-99m MIBI-negative but US-detected suspicious cervical nodules; therefore, the sample size was small. We collected only 15 cases throughout more than 8 years. There were no false-positive or false-negative results of UG-FNA in this study. We hope that with the increase in the number of cases, this conclusion will be confirmed.

In conclusion, our data suggest that cytological evaluation, immunohistochemical staining, and aspirate fluid PTH determination of UG-FNA were helpful for preoperative localization in Tc-99m MIBI-negative PHPT patients with US-detected suspicious parathyroid nodules and can be applied selectively or in combination. Aspirate fluid PTH determination should be preferred for nodules with cystic components. The small sample size in our study might preclude its applicability in routine clinical practice. Further prospective study with large population is needed to confirm our conclusions in the future.

References

- [1] Siperstein A, Berber E, Mackey R, et al. Prospective evaluation of sestamibi scan, ultrasonography, and rapid PTH to predict the success of limited exploration for sporadic primary hyperparathyroidism. *Surgery* 2004;136:872–80.
- [2] Akin M, Atasver T, Kurukahvecioglu O, et al. Preoperative detection of parathyroid adenomas with Tc-99m MIBI and Tc-99m pertechnetate scintigraphy: histopathological and biochemical correlation with Tc-99m MIBI uptake. *Bratisl Lek Listy* 2009;110:166–9.
- [3] Isik S, Akbaba G, Berker D, et al. Thyroid-related factors that influence preoperative localization of parathyroid adenomas. *Endocr Pract* 2011;8:1–21.
- [4] Berber E, Parikh RT, Ballem N, et al. Factors contributing to negative parathyroid localization: an analysis of 1000 patients. *Surgery* 2008;144:74–9.
- [5] Untch BR, Adam MA, Scheri RP, et al. Surgeon-performed ultrasound is superior to 99Tc-sestamibi scanning to localize parathyroid adenomas in patients with primary hyperparathyroidism: results in 516 patients over 10 years. *J Am Coll Surg* 2011;212:522–9.
- [6] Abraham D, Sharma PK, Bentz J, et al. Utility of ultrasound-guided fine-needle aspiration of parathyroid adenomas for localization before minimally invasive parathyroidectomy. *Endocr Pract* 2007;13:333–7.
- [7] Owens CL, Rekhman N, Sokoll L, et al. Parathyroid hormone assay in fine-needle aspirate is useful in differentiating inadvertently sampled parathyroid tissue from thyroid lesions. *Diagn Cytopathol* 2008;36:227–31.
- [8] Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000;343:1863–75.
- [9] Ciuni R, Ciuni S, Monaco G, et al. Parathyroid cyst. Case report. *Ann Ital Chir* 2010;81:49–52.
- [10] Kwak JY, Kim EK, Moon HJ, et al. Parathyroid incidentalomas detected on routine ultrasound-directed fine-needle aspiration biopsy in patients referred for thyroid nodules and the role of parathyroid hormone analysis in the samples. *Thyroid* 2009;19:743–8.
- [11] Erbil Y, Salmaslioglu A, Kabul E, et al. Use of preoperative parathyroid fine-needle aspiration and parathormone assay in the primary hyperparathyroidism with concomitant thyroid nodules. *Am J Surg* 2007;193:665–71.
- [12] Lieu D. Cytopathologist-performed ultrasound-guided fine-needle aspiration of parathyroid lesions. *Diagn Cytopathol* 2010;38:327–32.