

Usefulness of preoperative ultrasonographic localization for diagnosis of a rare disease

Intrathyroid parathyroid lesions

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Abstract

The aim of this article is to explore the value of ultrasonic diagnosis and localization of intrathyroid parathyroid diseases.

The medical records of 15 patients with surgically confirmed intrathyroid parathyroid diseases were reviewed. We analyzed the diagnosis process and recorded sonographic features of these intrathyroid parathyroid lesions.

The patients included 11 females (73%, 11/15) and 4 males (27%, 4/15) with a mean age of 46.2 ± 10.2 years and a mean lesion size of 2.1 ± 1.1 cm. A total of 11 intrathyroid parathyroid lesions in this study presented as hypoechoic (73.3%, 11/15). Nine lesions were located in the right lobe of the thyroid (60%, 9/15), and most of the lesions were located in the middle and inferior thyroid (80%, 12/15). All of the 15 intrathyroid parathyroid lesions were variable in shape and well defined. Only 1 lesion showed microcalcification, which was confirmed as parathyroid adenocarcinoma by the postoperative pathological diagnosis. The blood supply of 13 lesions was plentiful (86.7%, 13/15). A hyperechoic line on the parathyroid lesion was detected in 13 lesions (86.7%, 13/15). Based on the degree to which the parathyroid gland was embedded in the thyroid gland, 12 cases were classified as the complete type (80%, 12/15), and 3 cases were classified as the incomplete type (20%, 3/15). Ultrasound was used to diagnose 10 cases, and sestamibi-SPECT was used to diagnose 11 cases preoperatively; the 2 imaging methods were complementary.

Ultrasonic preoperative localization could be helpful in the diagnosis and management of intrathyroid parathyroid diseases.

Abbreviations: CT= computed tomography, sestamibi-SPECT = Tc-99m sestamibi -scintigraphy with single photon emission computed tomography.

Keywords: intrathyroid parathyroid gland, localization, ultrasonography

1. Introduction

Hyperparathyroidism exhibits a low incidence, approximately 0.1% to 0.4%.^[1] However, hyperparathyroidism caused by intrathyroid parathyroid lesions is rare, with an incidence of 1% to 3.4%^[2–4] among patients suffering from hyperparathyroidism^[5–7] such as renal osteodystrophy and renal calculus.^[8] Accurate diagnosis and preoperative localization of intrathyroid parathyroid lesions is important because surgically removing the focal lesions can be an effective method to cure hyperparathyroidism.^[9] Tc-99m sestamibi-scintigraphy with single photon

emission computed tomography (sestamibi-SPECT) has a high sensitivity for the diagnosis of intrathyroid parathyroid lesions, and it is the main lesion localization method. However, sestamibi-SPECT does not have satisfactory specificity, and its ability to identify sectional anatomy is not ideal. Ultrasound can be used as a first-line tool for the diagnosis and location of parathyroid lesions because it has the advantages of being economical, functioning in real time, and radiationless and can distinguish anatomical structures in cervical sections very well. However, the differential diagnosis between rare intrathyroid parathyroid lesions and common thyroid nodules can be difficult. Therefore, the purpose of this study was to evaluate the usefulness of preoperative ultrasonographic localization for diagnosis of lesions, to summarize the ultrasonographic characteristics of intrathyroid parathyroid lesions, and to provide a reference for the diagnosis and treatment of intrathyroid parathyroid lesions.

2. Patients and methods

2.1. Study patients

Between November 2003 and November 2013, 1060 patients underwent a parathyroidectomy due to hyperparathyroidism in our hospital. Clinical, pathologic, and imaging findings were retrospectively reviewed in this study. Of the total participants, 45 patients were diagnosed with ectopic parathyroid disease (4.25%, 45/1060), and 15 patients were diagnosed with intrathyroid parathyroid disease (1.4%, 15/1060). Among the 15 patients, 4 patients presented with a cervical mass, 1 presented with a prolactinoma, 2 presented with a parathyroid mass

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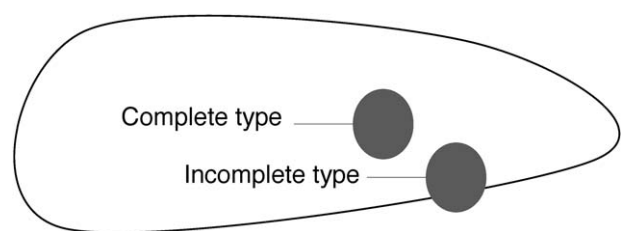


Figure 1. The long-axis ultrasound view of the thyroid gland shows that complete type lesions were completely wrapped by the thyroid and incomplete type lesions were >50% wrapped by the thyroid.

diagnosed in another hospital, and the remaining 8 patients presented with osteoporosis, hypercalcemia, bone-arthritis pain, urinary calculi and complaints of thirst. None of the 15 patients had a family history of parathyroid disease. The study was approved by the ethics review committee of the Peking Union Medical College Hospital. Due to the retrospective nature of the study, informed consent was not necessary, but personal data and confidentiality were top priority.

2.2. Ultrasound examination

The ultrasound apparatus consisted of a Philips iU22 (Philips Medical Systems, Bothell, WA), GE Logiq 9 (GE Healthcare, Milwaukee, WI), or Philips EsaoteDU6 (Philips Medical Systems, Bothell, WA) with a 5 to 12 MHz linear probe. Gray-scale and color Doppler ultrasonography were used to examine the thyroid. The patient was placed in a supine position with the neck exposed sufficiently to allow scanning of multiple sections of the parathyroid, which is located posterior to the thyroid gland, and the thyroid gland. Abnormalities of the parathyroid glands were recorded. Additionally, the size, border, shape, internal echo, calcification, hyperechoic line on the margins of the nodules and blood flow supplying the thyroid nodules were recorded. The internal echo was divided into 3 categories as follows: hypoechoic, mixed echo (an anechoic zone inside the lesion), and slightly increased echo. Calcification was divided into the following 2 categories: with calcification and without calcification; and blood flow was divided into 2 categories as follows: rich

and not rich. According to the degree to which the parathyroid gland was embedded in the thyroid gland, parathyroid lesions in this study were classified as either a complete type (lesions completely wrapped by the thyroid) or an incomplete type (most of the lesion wrapped by thyroid). It should be noted that if <50% of a lesion was wrapped by the thyroid, it was not regarded as an intrathyroid parathyroid lesion (Fig. 1).

2.3. Comparison of common imaging methods

The results of ultrasonography, sestamibi-SPECT, and CT were compared among 15 patients, and the value of the different methods used in the diagnosis of the intrathyroid parathyroid lesions was evaluated.

3. Results

3.1. General results

A total of 15 patients with intrathyroid parathyroid lesions were enrolled in this study, including 11 females (73%, 11/15) and 4 males (27%, 4/15) with a mean age of 46.2 ± 10.2 years. The parathyroid hormone (PTH) levels were higher than normal in these 15 patients. Fourteen patients had hypercalcemia, and 1 patient had a normal serum calcium level. The 15 patients included 12 cases of parathyroid adenoma (80%, 12/15), 1 case of parathyroid hyperplasia (6.7%, 1/15), and 2 cases of parathyroid adenocarcinoma (13.3%, 2/15) confirmed postoperatively. The mean size of the 15 lesions was 2.1 ± 1.1 cm (Table 1).

3.2. Specific location and sonographic features

A total of 9 lesions were located in the right lobe of the thyroid (60%, 9/15), 6 were located in the left lobe (40%, 6/15), 12 were located in the middle and inferior thyroid (80%, 12/15), and 3 were located superiorly (20%, 3/15). A total of 11 lesions presented as hypoechoic (73.3%, 11/15), 3 presented as mixed echo (20%, 3/15), and 1 presented as moderate echo (6.7%, 1/15). All 15 intrathyroid parathyroid lesions were well defined, and most were elliptical, lachrymiform, or leaflet-shaped. Only 1 lesion showed microcalcification, which was confirmed as

Table 1

Clinical, imaging and pathological information of 15 cases of intrathyroid parathyroid lesions.

No.	Pathology	PTH	Serum Ca	MIBI	US(P)	US(T)	Size, cm	Location	Echo	Blood	Shape	Border	Calcification	Hyperechoic line
1	AN	(+)	(+)	(+)	(-)	(+)	3.0 × 1.9 × 1.4	Rt I	Hypo	Rich	L	W	(-)	(+)
2	AN	(+)	(+)	(+)	(-)	(+)	1.3 × 0.7 × 0.6	Lt M	Hypo	Rich	E	W	(-)	(+)
3	AN	(+)	(+)	(+)	(-)	(+)	1.3 × 1.4 × 1.0	Rt S	Hypo	Rich	Lb	W	(-)	(+)
4	AN	(+)	(+)	(+)	(-)	(-)	1.5 × 0.8	Lt I	Hypo	Rich	E	W	(-)	(+)
5	AN	(+)	(+)	(+)	(-)	(+)	1.5 × 0.9	Lt M	Hypo	Rich	E	W	(-)	(+)
6	AN	(+)	(+)	(+)	(-)	(+)	2.6 × 1.2	Rt I	Hypo	Rich	Lb	W	(-)	(+)
7	AN	(+)	(+)	(-)	(-)	(+)	1.8 × 0.9	Lt I	Hypo	Little	L	W	(-)	(+)
8	AN	(+)	(+)	(+)	(-)	(+)	2.0 × 0.8 × 0.5	Rt M	Hyper	Rich	L	W	(-)	(+)
9	AN	(+)	(+)	(+)	(-)	(+)	1.4 × 0.5	Rt M	Hypo	Little	Lf	W	(-)	(+)
10	AN	(+)	(+)	(+)	(-)	(-)	4.1 × 2.3	Rt I	Mixed	Little	Lb	W	(-)	(-)
11	AN	(+)	(-)	(-)	(-)	(-)	2.8 × 1.9 × 1.1	Rt I	Mixed	Rich	E	W	(-)	(+)
12	HP	(+)	(+)	(+)	(-)	(+)	1.2 × 1.3 × 0.8	Rt M	Mixed	Rich	E	W	(-)	(+)
13	AC	(+)	(+)	UD	(-)	(-)	5.0 × 3.2 × 2.4	Lt I	Hypo	Rich	Lb	W	(-)	(-)
14	AC	(+)	(+)	UD	(-)	(-)	2.6 × 0.9 × 0.9	Rt S	Hypo	Rich	E	W	Punctate	(+)
15	AN	(+)	(+)	(+)	(-)	(+)	0.9 × 0.7 × 0.9	Lt S	Hypo	Rich	E	W	(-)	(+)

AC=adenocarcinoma, AN=adenoma, E=elliptical, HP=hyperplasia, I=inferior, L=lachrymiform, Lb=lobulated, Lt=left, M=middle, PTH = parathyroid hormone, Rt=right, S=superior, UD=undetectable, US(P)=parathyroid ultrasound, US(T)=thyroid ultrasound, W=well-defined.

parathyroid adenocarcinoma by postoperative pathological diagnosis. Doppler ultrasound signals indicated plentiful blood flow in 13 lesions (86.7%, 13/15), and 2 lesions had decreased blood flow (13.3%, 2/15). A hyperechoic line between the parathyroid lesion and thyroid tissue was detected in 13 lesions (86.7%, 13/15). A total of 13 lesions were classified as the complete type (80%, 12/15), and 3 cases were classified as the incomplete type (20%, 3/15). All the images were analyzed by 2 ultrasound physicians with over 10 years of experience and all the features of intrathyroid lesions were discussed.

3.3. Comparison of the results between different imaging examinations

Among the 15 patients, 5 cases (33.3%, 5/15) were diagnosed using ultrasound screening; however, 10 cases (66.7%, 10/15) were diagnosed by experienced ultrasound physicians after reexamination, and the results of sestamibi-SPECT were referenced in 13 cases. Among these 13 cases, 11 had positive results (84.6%, 11/13). The results of ultrasound and sestamibi-SPECT were not consistent. One case was positive using ultrasound but negative by sestamibi-SPECT; however, 2 cases were positive by sestamibi-SPECT but negative using ultrasound. When the results of ultrasound were combined with sestamibi-SPECT, the accuracy was 92.3% (12/13). A total of 3 patients underwent CT examination; however, no accurate results were obtained.

4. Discussion

Hyperparathyroidism caused by intrathyroid parathyroid lesions is rare, and few reports have described diagnosis by localization. Some scholars believe that when surgeons do not find the preoperatively suspected parathyroid gland lesions during surgery, ipsilateral thyroidectomy should be performed to assure that no potential intrathyroidal parathyroid lesions are present. Some scholars also believe it is not advisable to remove the thyroid gland directly without finding a definite lesion because the incidence of these lesions is low.^[10] Furthermore, blind thyroidectomy may cause hypothyroidism, and the symptoms of hyperparathyroidism may not be relieved. Therefore, accurate preoperative localization is important for the diagnosis of intrathyroid lesions, which is the main purpose of research into this rare disease.

Intrathyroid parathyroid lesions are difficult to locate. The superior and inferior parathyroid glands are usually paired. The superior parathyroid gland arises from the fourth branchial pouches, along with the lateral lobes of the thyroid gland. They are generally located on the dorsal aspect of the upper thyroid lobes at the level of the inferior border of the cricoid cartilage. The inferior parathyroid gland arises from the third branchial pouches, along with the thymus. The majority of inferior parathyroid glands reside at or immediately inferior to the posterior aspect of the lower pole of the thyroid. In fact, they can be located anywhere within the angle of the mandible and the upper mediastinum, even in thyroid tissue.^[11] The parathyroid gland is encapsulated in the thyroid gland during embryonic development, which may be the cause of ectopic parathyroid glands in the thyroid gland.^[2] In this study, most intrathyroid parathyroid lesions were located in the middle and inferior thyroid (80%, 12/15). It is likely that the inferior parathyroid gland is more prone to ectopic lesions due to a longer migration distance during development.

The intrathyroid parathyroid lesions were mostly hypoechoic; some were classified as mixed echo, and individual lesions were slightly hyperechoic. One study suggests that the characteristic hypoechoic appearance is caused by the hypercellularity and vascularity of the lesion, which has little fat content, which leaves few interfaces for reflecting sound.^[12] The pathological features of vascularity in the lesion and an enlarged extrathyroidal artery with abundant blood flow signals were found in 13 of the 15 lesions in our study. The internal cystic components, which may have resulted from cystic degeneration, showed mixed echoes.^[13] One atypical adenoma presented with a slightly higher echo, which may have been caused by various components of the lesion. Some adenomas may have increased fat and irregular fibrous components internally.^[14]

The incidence of thyroid nodules is high in the population; therefore, rare intrathyroid parathyroid lesions should be distinguished from common thyroid nodules. Other imaging methods like diffusion-weighted magnetic resonance imaging may be helpful in diagnosis of thyroid diseases,^[15-16] but there is no literature reporting that it can distinguish whether the nodules in the thyroid gland are derived from parathyroid glands. In addition to the characteristic of being hypoechoic with abundant blood flow signals as mentioned previously, a thin hyperechoic line was observed on the surface of 86.7% of intrathyroid lesions in this study, which is identical to the findings reported in the literature.^[17] This line may be the capsule echo of the thyroid and parathyroid glands. A halo was frequently observed around thyroid nodules, which may be caused by a rim of blood vessels around the adenoma or by compression of surrounding glandular tissue.^[18]

Rumack et al^[12] defined an intrathyroid parathyroid as parathyroid glandular tissue that is completely wrapped by the thyroid gland. They believed that parathyroid adenomas that lie under the pseudocapsule or sheath covering the thyroid gland or within a sulcus of the thyroid are not true intrathyroid adenomas. However, these adenomas may be difficult for the surgeon to visualize during surgery unless this sheath is opened. Moreover, the surgical method for parathyroid tissue that is wrapped by >50% of thyroid tissue is the same method used in clinical practice for parathyroid tissue that is completely wrapped by thyroid tissue. Partial resection of thyroid tissue is required to completely remove the lesion in the 2 types of parathyroid lesions described previously, which is dependent on the experience of the surgeon and supported in the literature.^[19] Therefore, in our study, we defined parathyroid lesions that were >50% wrapped by thyroid tissue as the incomplete type of intrathyroid parathyroid lesion (20%, 3/15), and parathyroid lesions that were 100% wrapped by thyroid tissue were defined as the complete type (80%, 12/15). Sonographers should provide more accurate information for the clinician for patients who are clinically suspected of having parathyroid lesions that are >50% wrapped by thyroid tissue.

Ultrasonographic diagnosis and localization of intrathyroid parathyroid glands depends on the experience of the ultrasound physicians. The results of our study showed that the accuracy of the reexamination was higher than that of the initial examination. The results of sestamibi-SPECT can serve as a reference for reexamination by an experienced senior ultrasound physician.

Sestamibi-SPECT, as a functional imaging mode for the parathyroid, is helpful for the diagnosis of parathyroid lesions. However, it has limited effectiveness in the preoperative location of lesions due to its unsatisfactory ability to determine sectional anatomical information. In this study, the results of ultrasound

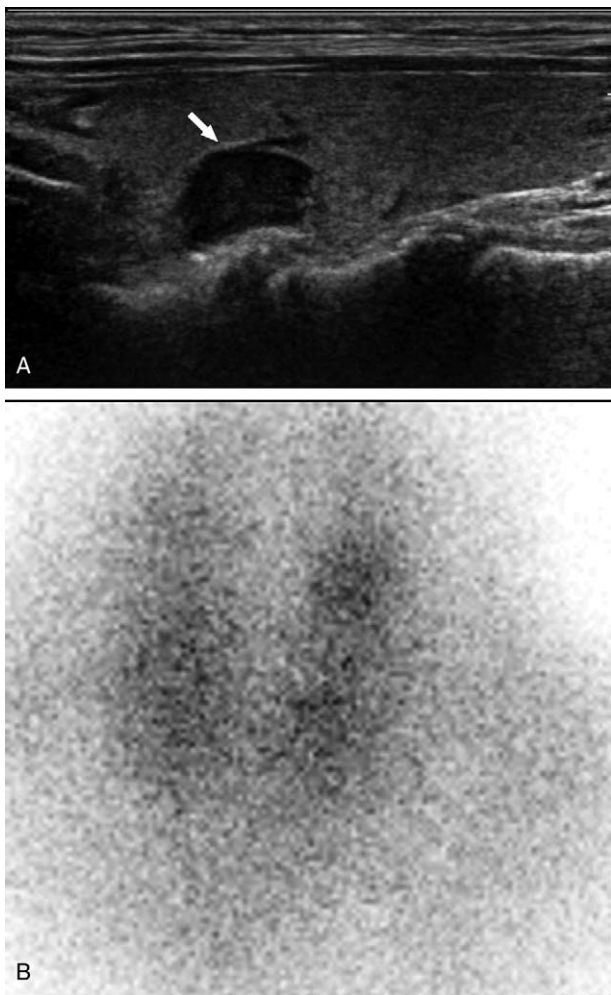


Figure 2. The imaging results of a 67-year-old female with primary hyperparathyroidism are shown. (A) B-mode ultrasonography shows a well-defined, lobulated, hypoechoic nodule located in the superior thyroid. A hyperechoic line is clearly detected (arrow). (B) Dual-phase scintigraphy of sestamibi-SPECT shows an area with increased radiation in the superior left lobe of the thyroid and is considered to be a hyperactive parathyroid gland.

and sestamibi-SPECT were not consistent. One case was positive on ultrasound but negative by sestamibi-SPECT; however, 2 cases were positive by sestamibi-SPECT but negative on ultrasound. The combination of ultrasound and sestamibi-

SPECT can improve the diagnostic accuracy of intrathyroid parathyroid lesions.^[20] Sestamibi-SPECT has a high sensitivity and low specificity for the intrathyroid parathyroid. Therefore, we suggest that patients with suspicious intrathyroid parathyroid lesions first undergo sestamibi-SPECT and then undergo an ultrasound examination to accurately locate the lesion. Ultrasound can provide more sectional anatomy information such as size and the relationship between the lesion and the surrounding tissue. Bahar^[4] and Proye^[21] reported that the sensitivity of ultrasound for detecting intrathyroid parathyroid lesions were 67% and 57%, respectively. Roy^[22] reported that the diagnostic accuracy of ultrasound was 53%, the accuracy of sestamibi-SPECT was 76%, and the accuracy of the combination of the 2 methods was 81%. In our research, the diagnostic accuracy of ultrasound and sestamibi-SPECT were 66.7% and 84.6%, respectively, and the combined accuracy of the 2 methods was 92.3%. The combination of the 2 methods can provide information about the origin, location, and size of the lesion and the relationship with surrounding tissues, which can significantly improve the diagnosis of intrathyroid parathyroid lesions.

Due to the analysis and summary of 15 cases of intrathyroid parathyroid lesions, we diagnosed 2 cases accurately in the previous 7 months. The 2 patients presented to our hospital for osteoporosis and hypercalcemia with high PTH levels. No significant abnormality was observed in the normal area of the parathyroid in the initial ultrasound examination. Upon reexamination, we observed a hypoechoic nodule in the thyroid with plentiful blood flow signals, and a hyperechoic line between the parathyroid and thyroid tissue was observed. Based on the sestamibi-SPECT results, we determined that the lesion was located at the same level as that reported by ultrasound. We confidently diagnosed the 2 patients with intrathyroid parathyroid lesions. The 2 cases were confirmed by postoperative pathology (Figs. 2 and 3). Thus, due to our understanding of this rare disease, its diagnosis will gradually become common.

This study examined 15 cases of intrathyroid parathyroid lesions that were confirmed by surgery in our hospital from March 2003 to November 2016. Future multicenter clinical studies are expected to include a larger sample size.

Author contributions

Data curation: Tiantian Ye, Xuepei Huang.

Investigation: Ya Hu, Quan Liao.

Methodology: Liang Wang, He Liu.

Project administration: Yu Xia, Yuxin Jiang.



Figure 3. The pathology and histopathology results of a 53-year-old female with hypercalcemia and bone-arthritis pain are shown. (A) B-mode ultrasonography shows a well-defined, elliptical, hypoechoic nodule located in the inferior thyroid. A hyperechoic line is clearly detected (arrow). (B) The gross pathology specimen shows parathyroid lesions (yellow) and thyroid tissue (red). (C) Histopathological images confirm that the lesion is an intrathyroid parathyroid adenoma (hematoxylin and eosin-stained tissue; magnification, $\times 50$).

Resources: Yu Xia.

Supervision: Yuxin Jiang.

Validation: Li Huo.

Visualization: Bo Zhang.

Writing – original draft: Tiantian Ye, Xuepei Huang.

Writing – review & editing: Tiantian Ye, Xuepei Huang, Li Ma, Xingjian Lai, Ke Lv.

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