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Ultrasonographic features of intrathyroidal parathyroid adenoma causing primary hyperparathyroidism

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Abstract. Preoperative localization study is difficult in patients with primary hyperparathyroidism (PHPT) caused by intrathyroidal parathyroid adenoma. The objective of this study was to evaluate the usefulness of ultrasonography (US) in the diagnosis of intrathyroidal parathyroid adenoma. Between January 2004 and December 2009, seven of 373 patients who underwent parathyroidectomy because of PHPT in our hospital were found to have intrathyroidal parathyroid adenoma. The ultrasonographic features of intrathyroidal parathyroid adenoma were examined retrospectively. The most characteristic feature of intrathyroidal parathyroid adenoma was a hyperechoic line on the ventral surface of the parathyroid gland. A hyperechoic line was clearly detected even in small adenomas in which feeding vessels could not be detected on color Doppler sonography. In comparison with feeding vessels, a hyperechoic line was frequently detected in normally located parathyroid adenoma. ^{99m}Tc-sestamibi (MIBI) scintigraphy and computed tomography (CT) could show parathyroid adenoma in the intrathyroidal position in only three of five and in only one of three patients examined, respectively. Since a hyperechoic line is characteristic of parathyroid adenoma, an intrathyroidal parathyroid adenoma could be suspected by only non-invasive US.

Key words: Intrathyroidal parathyroid adenoma, Primary hyperparathyroidism, Ultrasonography

PARATHYROID adenoma can be detected by ultrasonography (US), computed tomography (CT) and other imaging studies, since most parathyroid glands exist in the normal location; however, in the case of an ectopic gland, especially intrathyroidal parathyroid adenoma, an abnormal gland may be considered as one of the nodules in the thyroid gland. Among patients with thyroid nodules, primary hyperparathyroidism (PHPT) may be noted incidentally by the existence of hypercalcemia. When hypercalcemia was recognized, PHPT could be diagnosed by serum PTH measurement, and in addition to routine US, further ^{99m}Tc-sestamibi (MIBI) scintigraphy, CT and other imaging techniques could suggest the location of parathyroid adenoma, even if an abnormal gland was encased within a thyroid gland [1, 2]; however, without information about hypercalcemia, it has been very difficult to distinguish intrathyroidal parathyroid adenoma from adenomatous nodule in the thyroid gland by routine cervical exploration of US [3].

Recently, high-resolution US has made it possible to provide more detailed information, and plays an important role in the localization of the abnormal parathyroid gland. The purpose of this study was to elucidate the characteristic ultrasonographic features of intrathyroidal parathyroid adenoma in our cases and to evaluate the role of cervical US in parathyroid adenoma.

Patients and Methods

Between January 2004 and December 2009, 373 patients underwent parathyroidectomy because of PHPT. Of these, 327 patients were diagnosed with parathyroid adenoma by pathological examination. Seven patients (2.1%) were found to have parathyroid adenoma partially or entirely encased within the thyroid tissue. These patients consisted of six females

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Table 1 Characteristics of patients with intrathyroidal parathyroid adenoma

Patient	1	2	3	4	5	6	7
Age at surgery/Gender	69/F	73/F	55/F	78/F	77/M	70/F	39/F
Location	Lt L	Rt L	Lt U	Rt L	Rt U	Rt L	Lt L
Ca (mg/dL)	10.1	12.5	10.5	11.4	10.9	11.2	11.6
i-PTH (pg/mL)	117*	263	210*	100	838	157	186
Preoperative US evaluation	AN	PT	M	PT	AN	PT	PT
MIBI scintigraphy	–	D	–	UD	D	D	UD
CT	–	–	–	–	D	D	UD
Preoperative diagnosis	ML	PHPT	FT	PHPT	PHPT	PHPT	PHPT
Operation	Lt PL	Rt PL	ST	Rt PL	Rt PL	Rt PL	Lt PL

* Preoperative i-PTH level was measured using conserved serum.
Lt, left; Rt, right; L, lower; U, upper; AN, adenomatous nodule; PT, parathyroid tumor; M, malignant tumor; UD, undetectable; D, detectable; ML, malignant lymphoma; PHPT, primary hyperparathyroidism; FT, follicular tumor; PL, partial thyroid lobectomy; ST, subtotal thyroidectomy

Table 2 Ultrasonographic findings of intrathyroidal parathyroid adenoma

Patient	1	2	3	4	5	6	7
Size	10mm	12mm	19mm	5mm	12mm	14mm	14mm
Shape	regular	regular	irregular	regular	regular	irregular	regular
Border	smooth	smooth	jagged	smooth	smooth	jagged	smooth
Internal echo	hypo	hypo	hypo	hypo	hypo	hypo	hypo
Hyperechoic line	UD	D	D	D	D	D	D
Feeding vessels	UD	D	D	UD	D	D	D

UD, undetectable; D, detectable

and one male aged from 39 to 78 years (Table 1). Ultrasonographic features of parathyroid adenoma were examined retrospectively in these patients.

The ultrasound apparatus used was Aloka Pro Sound SSD-5500 (Aloka, Tokyo, Japan) with UST-5712 (10 MHz) and UST-5543 (13 MHz) linear probes, and Aplio 80 (Toshiba, Tokyo, Japan) with PLT-1204AX (7-14 MHz) and PLT-805AT (5-12 MHz) linear probes. Ultrasonographic examinations were performed by well-trained registered medical sonographers. To minimize interobserver variation, these sonographers underwent at least 3 months of training in our department to accurately evaluate ultrasonographic findings at neck exploration. Furthermore, evaluations were made by at least two sonographers before surgery. Based on our experience, we established a classification system for ultrasonographic evaluation of thyroid nodules, as we reported previously [4]. This system was used for the study population. Each patient was placed in the sitting position with the neck hyperextended and then transverse and longitudinal views were recorded. Parathyroid scintigraphy was performed using a dual-head gamma camera (Infinia; GE Healthcare, Tokyo, Japan). CT scan was performed using a multislice X-ray CT scanner (Asteion Super4; Toshiba, Tokyo, Japan), and slice thickness was 3mm in selected patients.

Tables 1 and 2 summarize the characteristics and ultrasonographic findings of patients with intrathyroidal parathyroid adenoma, respectively. In two of seven patients (patients 1 and 3), because of only mild hypercalcemia and no symptoms, primary hyperparathyroidism was not suspected preoperatively; thus, the intact PTH level was not measured, and MIBI scintigraphy and CT were not performed. In these patients, US-guided fine-needle aspiration biopsy (FNAB) was erroneously interpreted as suspected malignant lymphoma and suspected follicular tumor, respectively. Three of seven patients (patients 2, 4 and 5) were referred to our hospital for further examination of hypercalcemia, and patients 6 and 7 for thyroid nodule and chronic thyroiditis, respectively. Since these five patients showed hypercalcemia and a high intact PTH level, surgical resection was performed for suspected parathyroid adenoma. MIBI scintigraphy and CT were performed in five and three of these patients, respectively (Table 1).

Patient 1 had a nodule which was erroneously diagnosed as suspected malignant lymphoma on FNAB;

therefore, partial lobectomy was performed for definitive diagnosis. Patient 3 had a nodule in the left lobe of the thyroid that was interpreted as follicular tumor on FNAB. Since she also had an adenomatous nodule in the contralateral lobe, subtotal thyroidectomy was performed. In patients 2, 4, 5, 6 and 7 who were preoperatively diagnosed with PHPT, partial resection of the lobe containing a parathyroid tumor was performed based on preoperative findings of US and/or CT. Intrathyroidal parathyroid adenoma in patient 2 was confirmed by intraoperative pathological diagnosis. In patient 4, partial resection of the lower pole of the right thyroid lobe including a nodule was performed. The lesion was diagnosed as adenomatous nodule by intraoperative frozen section. Despite extended cervical explorations, we could not find a parathyroid adenoma; however, the intraoperative i-PTH level decreased to the normal range after partial lobectomy, and intrathyroidal parathyroid adenoma was confirmed by final pathological examination.

To investigate the performance of US in distinguishing intrathyroidal parathyroid adenoma from adenomatous nodule of the thyroid, patients who underwent thyroidectomy for papillary thyroid carcinoma associated with adenomatous nodules were randomly selected. As the comparison group, we selected 20 nodules of <20mm and histologically confirmed as adenomatous nodule. Furthermore, in 50 randomly selected patients who underwent focused parathyroidectomy in our hospital because of normally located parathyroid adenoma, the frequency of a hyperechoic line and feeding vessels on preoperative US was compared.

The chi-square test and Fisher's exact test were employed to analyze the variables. Significance was set at $p<0.05$.

Results

Ultrasonographic features of intrathyroidal parathyroid adenoma were reviewed retrospectively in the seven patients. On B-mode US, intrathyroidal parathyroid adenoma was a hypoechoic solid mass in all seven patients, and had a smooth border and regular tumor shape in five of seven patients (Table 2). A hyperechoic line on the ventral surface of intrathyroidal parathyroid adenoma was observed in six of seven patients (Fig. 1). On color Doppler sonography, a blood supply from feeding vessels was seen in five of seven patients.

MIBI scintigraphy showed MIBI accumulation in

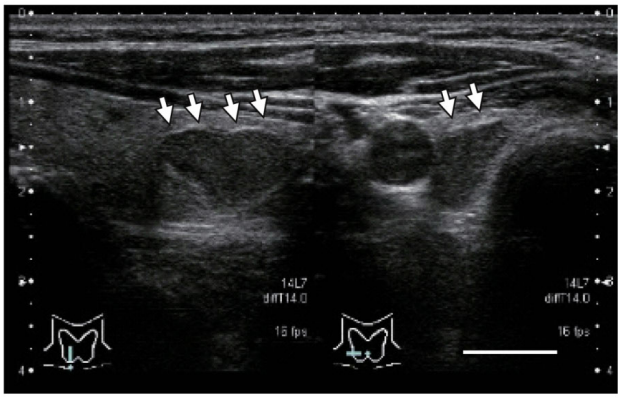

Fig. 1 Intrathyroidal parathyroid adenoma in right inferior position (Patient 6). Hyperechoic line between the parathyroid and thyroid gland is shown (arrow). Scale bar, 10mm

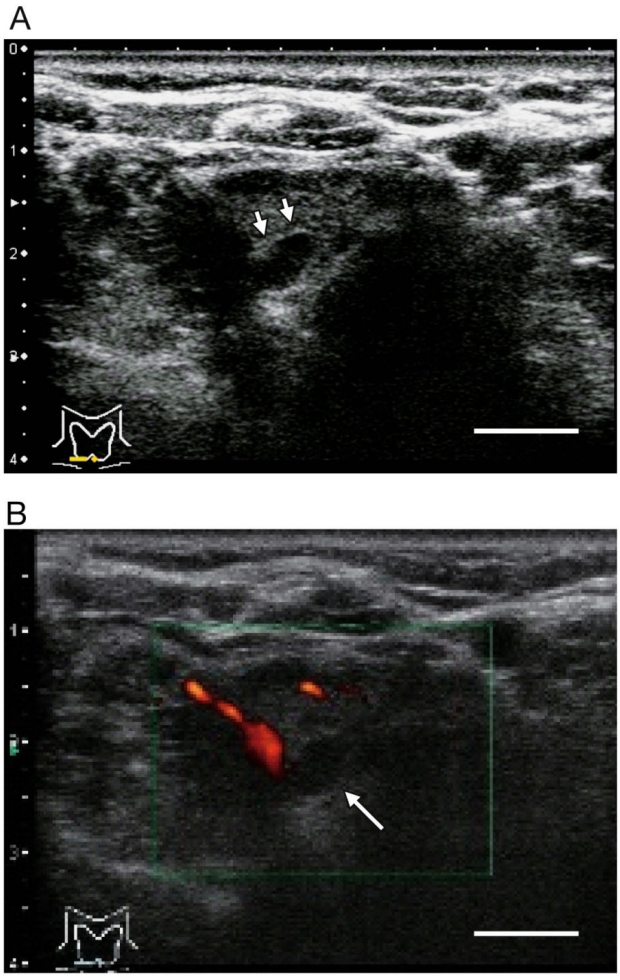

Fig. 2 Ultrasonograms of intrathyroidal parathyroid adenoma (Patient 4). Scale bar, 10mm. A. B-mode ultrasonogram. Hyperechoic line is clearly detected (arrow), although the adenoma is 5mm in diameter. B. Power Doppler ultrasonogram. Arrow shows intrathyroidal parathyroid adenoma. Feeding vessels were not identified.

Table 3 Comparison of US findings of intrathyroidal parathyroid adenoma with adenomatous nodule of the thyroid

US findings	Adenomatous nodule (n=20)	Intrathyroidal parathyroid adenoma (n=7)	
Shape			
Regular	18	5	N.S.
Irregular	2	2	
Border			
Smooth	16	5	N.S.
Jagged	4	2	
Internal echo			
Hypo	6	7	p=0.002
Iso	14	0	
Hyperechoic line			
Detectable	0	6	p<0.001
Undetectable	20	1	
Color Doppler US pattern			
Feeding vessel like	1	5	
Capsular pattern	7	0	p=0.001
Unclear	12	2	

N.S., not significant

intrathyroidal parathyroid adenoma in only three of five patients examined. CT scans of the neck revealed a nodule, shown as a low density mass within the thyroid gland in patients 5 and 6. Since the characteristic features of parathyroid tumor on CT are unknown, it was difficult to consider the intrathyroidal nodule as a parathyroid tumor using CT scans only. In patient 7, neither MIBI scintigraphy nor CT scans could detect a suspected parathyroid tumor.

Ultrasonographic features were compared between intrathyroidal parathyroid adenoma and adenomatous nodule of the thyroid (Table 3). A hyperechoic line in front of nodular lesions was detected only in patients with intrathyroidal parathyroid adenoma. In all patients except for patient 1, a hyperechoic line was detected in each preoperative evaluation, which two sonographers independently made (Cohen's kappa coefficient, 1.0). None of the 20 thyroid nodules showed a hyperechoic line in front of nodules. Thus, sensitivity and specificity for this characteristic finding in the ultrasonographic diagnosis of intrathyroidal parathyroid adenoma were 86% and 100%, respectively. Adenomatous nodule was detected as isoechoic or hypoechoic mass. Blood flow of the adenomatous nodule was frequently undetectable; if seen, it was detected as a peripheral pattern. Shape and border did not significantly differ between intrathyroidal parathyroid adenoma and adenomatous nodule.

Of 50 patients with normally located parathyroid adenoma, the hyperechoic line and feeding vessels were detected in 37 (74%) and 35 (70%) patients, respectively. The difference was not statistically significant. A hyperechoic line was frequently detected between the thyroid gland and parathyroid adenoma adjacent to the thyroid gland on its dorsal side. Of 40 patients, except for those with parathyroid adenoma located away from the thyroid gland, the hyperechoic line and feeding vessels were detected in 37 (93%) and 26 (65%) patients, respectively (p=0.003).

Discussion

Intrathyroidal parathyroid adenoma at primary cervical exploration was identified at rates of 1.4% to 3.4% [5-7]. In our study, 2.1% of patients diagnosed with parathyroid adenoma had PHPT due to intrathyroidal parathyroid adenoma. In the case of mild hypercalcemia, patients with intrathyroidal parathyroid adenoma may be just followed up without surgery because of the difficulty of localization; thus, the sensitivity of the US features would be overestimated. However, localization of parathyroid adenoma in a mild form of PHPT is often difficult, even if the adenoma is not ectopic. Since this bias can lead to overestimation of the sensitivity of diagnostic imaging other than US, it is difficult to identify the exact sensitivity of all imaging studies.

The typical sonographic appearance of intrathyroidal parathyroid adenoma in this study presented with a regular shape, smooth border, hypoechoic level of

internal echo, solid content, a hyperechoic line on the ventral surface of the parathyroid gland, and the presence of feeding vessels. A hyperechoic line between the parathyroid and thyroid gland represents the very thin capsules of both the parathyroid and thyroid glands. It is presumed that a hyperechoic line is produced by the strong reflection of ultrasound in the layer where the parathyroid gland is histologically separated from the thyroid tissue. Thus, a hyperechoic line is a characteristic finding of not only intrathyroidal parathyroid adenoma, but also normally located parathyroid adenoma dorsal to and adjacent to the thyroid gland. A hypoechoic halo is frequently seen in thyroid nodules and may be caused by a rim of blood vessels or by compression of the surrounding glandular tissue [3]. Except for calcification, the peripheral rim of a thyroid nodule is not represented by a hyperechoic line. This point is very important for differentiating intrathyroidal parathyroid adenoma from thyroid nodules.

The usefulness of color Doppler sonography for detecting intrathyroidal parathyroid adenoma has often been reported [5,8,9]; however, it was difficult to detect the feeding vessels in small parathyroid adenoma. In these patients, a hyperechoic line might be detectable between the parathyroid adenoma and thyroid gland. In patient 4, a hyperechoic line was clearly detected, although feeding vessels were not visualized on color Doppler sonography (Fig. 2). Recognition of a hyperechoic line was more valuable for detecting intrathyroidal parathyroid adenoma than the feeding vessels.

MIBI scan and CT are useful for detecting parathyroid adenoma, especially in the localization of ectopic adenoma. In our series, MIBI imaging was available for five of seven patients, and an abnormal gland could be detected in only three. Since a normal thyroid gland or thyroid nodule also takes up this radioisotope, it might be difficult to detect an abnormal parathyroid gland within the thyroid gland. Recently, the usefulness of single photon emission computed tomography (SPECT)/CT was reported [10]. Since parathyroid adenoma was not detectable on the planar image in two patients (patients 4 and 7), we also performed a combined SPECT/CT scan; however, additional useful information was not available (data not shown).

Measurement of the PTH level in percutaneous needle aspirates of the suspicious cervical mass was valuable for the diagnosis of parathyroid adenoma [11, 12]. In our two patients (patients 1 and 3), PTH levels in aspirates were helpful for differential diagnosis between the thyroid nodule and parathyroid adenoma, although cytological diagnosis was difficult. PTH assay using needle aspirates has one possible problem in that needle track dissemination of parathyroid cells may occur. Recurrence of parathyroid adenoma related to needle aspiration has not been reported; however, it should be performed only if localization of the adenoma is missed by non-invasive study.

In our hospital, the serum calcium level is routinely measured in the first examination. Thus, in patients with hypercalcemia, measurement of the PTH level and diagnostic imaging could be performed for suspected hyperparathyroidism; however, if hypercalcemia is not noticed, it is difficult to identify parathyroid adenoma, especially in an ectopic position. If the characteristic features of intrathyroidal parathyroid adenoma shown in the present study are understood sufficiently, an intrathyroidal parathyroid adenoma may be suspected by routine US. In 2 of the 7 patients, our sonographers identified the intrathyroidal position of the abnormal parathyroid gland without information about hypercalcemia. To date, there have been no false positives; however, it is important to suspect parathyroid abnormality, thereafter diagnosed by measurement of the serum calcium and PTH level. In the differential diagnosis between parathyroid adenoma and thyroid nodules, non-invasive US may be the most useful imaging technique.

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