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Parathyroid disorder and concomitant thyroid cancer in patients with multiple endocrine neoplasia type 1

A retrospective cohort study

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Abstract

This study aimed to determine the rates and characteristics of parathyroid disorder and thyroid cancer in patients with multiple endocrine neoplasia type 1 vs sporadic primary hyperparathyroidism (SPHP) undergoing parathyroidectomy.

Patients with multiple endocrine neoplasia type 1-associated primary hyperparathyroidism (MPHP) or SPHP who underwent initial or reoperative parathyroid exploration from 1999 to 2019 were identified via a clinical database. The data for MPHP patients (n = 15) were compared to those of a selected 2:1 age- and sex-matched SPHP cohort (n = 30) who all underwent thyroidectomy for concurrent thyroid nodules.

Compared with that of the SPHP group, the parathyroid hormone level of the MPHP group was much higher (470.67 ± 490.74 pg/mL vs 217.77 ± 165.60 pg/mL, $P = .001$). Multiglandular parathyroid disease (6/15 [40%] vs 3/30 [10%], $P = .026$) and more hyperplasia (7/15 [46.7%] vs 5/30 [16.7%], $P = .039$) were found in the MPHP group, and more parathyroid lesions presented as a round shape (long/short meridian < 2) by ultrasound (16/20 [80%] vs 8/31 [25.8%], $P < .001$). Regarding thyroid nodules, there was no difference in the rate of histologic thyroid cancer, but more thyroid cancer was found in the last 5 years among the MPHP cases (5/9 [55.6%] vs 3/18 [16.7%], $P = .052$).

Multiglandular parathyroid disease and hyperplasia were more frequent in the MPHP cohort than in the SPHP cohort, and the parathyroid lesions usually presented with a round shape on ultrasonography. More concurrent thyroid cancer was found in MPHP than SPHP patients over the previous 5 years.

Abbreviations: MEN1 = multiple endocrine neoplasia type 1, MPHP = MEN1-associated PHP, pHPT = primary hyperparathyroidism, SPHP = sporadic primary hyperparathyroidism.

Keywords: hyperparathyroidism, multiple endocrine neoplasia type 1, thyroid nodule, ultrasound

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) syndrome is an autosomal dominant inherited disorder characterized by a predisposition to the combined occurrence of multiple endocrine tumors.[1,2] The parathyroid glands, anterior pituitary glands, and pancreatic islets are involved in most cases. Primary hyperparathyroidism (pHPT) is the most common endocrinopathy in MEN1, and parathyroidectomy is recommended for patients who are symptomatic.[3,4] For both endocrinologists and endocrine surgeons treating patients with MEN1, evidence regarding the clinical relevance of thyroid tumors is meaningful. At present, several studies have determined the prevalence of

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Written informed consent was obtained from individual participants or their guardians.

This study was approved by the Institutional Ethics Committee of Peking Union Medical College Hospital (S-K1318).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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thyroid tumors in MEN1 patients. Case series with coexisting thyroid cancer and parathyroid disorders have been described in several studies.[3,5–7] The recently published MEN1 guidelines reported that thyroid tumors occur in more than 25% of patients with MEN1. Large epidemiologic studies have demonstrated the increased risks for malignancy, including thyroid cancer, in pHPT patients.[3,6,7]

Additionally, patients with MEN1 generally have enlargement of several parathyroid glands.[8–10] Ultrasonography is a first-line technique for imaging enlarged parathyroid glands of MEN1 patients and thyroid glands; however, only a few studies have examined parathyroid and thyroid glands in MEN1 patients with ultrasonography.[11–14]

Here, the aim of this study was to assess the prevalence of thyroid incidentalomas in the MEN1 population compared with a matched reference group of non-MEN1 patients. Additionally, we studied this particular population of patients who underwent preoperative neck ultrasonography to obtain clinically useful information that might aid the diagnosis of enlarged parathyroid glands.

2. Materials and methods

2.1. Patient inclusion/exclusion and data collection

This study was approved by the Institutional Ethics Committee of Peking Union Medical College Hospital (S-K1318). We retrospectively reviewed all parathyroid surgeries for pHPT performed between January 1999 and December 2019. The inclusion criteria were a diagnosis of either sporadic primary hyperparathyroidism (SPHP) or MEN1-associated PHP (MPHP) and concurrent thyroidectomy due to thyroid nodules. Primary hyperparathyroidism (PHP) diagnosis was defined by biochemical criteria, including a repeatedly increased or high-normal parathyroid hormone level. Diagnosis of MEN1, and therefore inclusion in the MPHP cohort, was based on fulfillment of clinical criteria (2 or more primary MEN1 tumors or 1 MEN1-associated tumor in a patient with a family member with MEN1) and/or by positive mutational testing.[15] Among 271 patients with MPHP, 33 had concurrent thyroid nodules diagnosed by ultrasonography, and 20 were surgically treated for MEN1; concurrent thyroidectomy was initially included. Five patients were excluded according to the following exclusion criteria: parathyroid malignancy (3 patients) or incomplete data (2 patients). Thus, 15 MPHP cases with concurrent thyroidectomy were eligible for the study. For comparative analysis, from 186 SPHP patients who underwent concurrent thyroidectomy in the database, a cohort of 30 patients was constructed by matching SPHP patients 2:1 by sex and by age at surgery to the MPHP patients. For both groups, a retrospective review was then performed to collect clinical information, preoperative imaging data including ultrasonographic features, preoperative laboratory data, indications for thyroidectomy, extent of surgery, and pathological data of the parathyroid and thyroid gland disorders. The reason for thyroidectomy was the coexistence of solitary or multiple thyroid nodules, discovered before surgery and accompanied by compressive or esthetic complaints, followed by incidental intraoperative findings. Surgical intervention on the thyroid varied from spreading of the observed lesions from adenomectomy and/or hemithyroidectomy to subtotal or total thyroidectomy. In addition, concurrent thyroidectomy was coded as either unplanned or planned.

2.2. Preoperative ultrasound examinations

After establishing the diagnosis of PHP biochemically, preoperative localization was performed by using ultrasound at the institution at the time. From 2005, routine ultrasound was added both for localization and to identify concomitant thyroid disease. In recent years, high-definition ultrasound examinations have been performed with Phillips HDI 5000, IU 22, GE Logiq 9 or Logiq 7 devices equipped with either a 5 to 12 MHz or an 8 to 15 MHz linear-array transducer. Ultrasound images were retrospectively reviewed by 2 radiologists who were experienced in the thyroid and parathyroid gland and blinded to the patients' clinical data and pathological results. Any inconsistencies were discussed until agreements were reached. Data on ultrasound features, namely, nodule shape (regular, irregular, taller-than-wide shape), margin (smooth, infiltrative, irregular), sonographic features (hyperechoic, isoechoic, hypoechoic, anechoic), internal structure (solid, partially solid, purely cystic), calcification (none, microcalcification, coarse calcification), and blood flow imaging, were also collected.[16]

2.3. Statistical analysis

Quantitative data are presented as the means ± standard deviations. Qualitative data are presented as frequencies. Data analysis was performed to compare the 2 groups, with Student *t* tests for continuous data and Fisher exact tests for categorical data. Descriptive statistics for continuous variables are expressed as the means ± standard deviations. The statistical analyses were performed with SPSS (version 19.0, SPSS Chicago, IL) software.

3. Results

As described above, for 15 patients in the MPHP cohort, a 2:1 age- and sex-matched SPHP cohort (n = 30) was selected. Sex and age distributions for both cohorts are included in Table 1. Only 1 MPHP patient had more than 1 thyroid operation. Compared with the SPHP group, the MPHP group had a much higher parathyroid hormone level (470.67 ± 490.74 pg/mL vs 217.77 ± 165.60 pg/mL $P = .001$).

By preoperative ultrasound, the overall preoperative detection rate of informal parathyroid glands by ultrasound was 91.2% (51/56 glands). The detection rate was 87% in MPHP cases (20/23 glands) and 93.9% in SPHP cases (31/33 glands), and there was no statistically significant difference between the 2 groups ($P = .33$). As seen in Figure 1, more parathyroid lesions presented as a round shape (long/short meridian < 2) (80%: 16/20 glands) in the MPHP group than in the SPHP group (25.8%: 8/31 glands); this difference was statistically significant ($P < .001$).

Regarding other ultrasonic features of parathyroid lesions, there were no differences between the 2 groups, as shown in Table 2. A total of 51 parathyroid glands were surgically removed, 20 glands in the MPHP group and 31 glands in the SPHP group. Compared with the SPHP group, the MPHP group had a higher frequency of multiglandular parathyroid disease (40%: 6/15 cases vs 10%: 3/30 cases, $P = .026$) and more hyperplasia (46.7%: 7/15 glands vs 16.7%: 5/30 glands, $P = .039$). Additionally, among 7 hyperplasia cases, 5 (71.4%) were multiglandular.

Considering that the ultrasonographic features of the parathyroid gland may be related to different pathologies, we further analyzed the ultrasonographic features in cases with different pathologies, parathyroid hyperplasia, and adenoma. The results

Table 1

Clinical characteristics of MPHP and SPHP patients.

	MPHP group N = 15	SPHP group N = 30	*P*
Female (%)	4 (26.7%)	8 (26.7%)	.632
Mean age at thyroidectomy (yr)	52.87 ± 9.92	53.43 ± 9.20	.896
PTH level (pg/mL)	470.67 ± 490.74	217.77 ± 165.60	**.001**
Patients with thyroidectomy during initial parathyroidectomy (%)	14/15 (93.3%)	30/30 (100%)	.333
Patients with thyroidectomy at reoperative parathyroidectomy (%)	1 (6.7%)	0 (0%)	
Patients with total thyroidectomy (or bilateral lobectomy) during the study period (%)	3/15 (20%)	6/30 (20%)	.661
Patients with preoperatively unplanned thyroidectomy (%)	6/15 (40%)	12/30 (40%)	.629
Preoperative detection rate of informal parathyroid glands (%)	20/23 (87%)	31/33 (93.9%)	.33
Multiglandular parathyroid disease (%)	6/15 (40%)	1/30 (10%)	**.003**
Mean parathyroid lesion numbers	1.6 ± 0.91	1.1 ± 0.55	**.002**
Informal parathyroid gland size (cm)	1.68 ± 0.78/24	1.88 ± 0.73/33	.349
Parathyroid hyperplasia (%)	7/15 (46.7%)	5/30 (16.7%)	**.039**
With concomitant thyroid cancer in 20 yr (%)	5/15	7/30	.355
With concomitant thyroid cancer in 5 yr (%)	5/9	3/18	**.052**
Thyroid nodule size (cm)	1.18 ± 0.73	1.16 ± 0.80	.968
Thyroid multiglandular (%)	3/5 (60%)	1/7 (14.3%)	.152

MEN1 = multiple endocrine neoplasia type 1, MPHP = MEN1-associated PHP, PTH = parathyroid hormone, SPHP = sporadic primary hyperparathyroidism.
Bold value represent significant difference.

showed that round shape was a significant ultrasound characteristic in MPHP cases with pathology of hyperplasia and those with pathology of adenoma ($P = .14$ and .018, respectively). When we compared the shape among all cases per hyperplasia and adenoma, the round shape was not significant ($P = .186$).

Twenty cases (71.4%) were complicated by the presence of thyroid adenomatous nodules. There was no difference in the rate of indications for thyroidectomy or extent of surgery between the 2 groups. In both groups, unplanned thyroidectomy was 40%, and there was no difference according to the cohort. The difference in preoperative thyroid ultrasonic features between thyroid nodules in MPHP patients and those in SPHP patients was not significant, as shown in Table 2. The histological thyroid cancer rate was higher in the MPHP group (33.3%: 6/15 cases) than in the SPHP group (23.3%: 7/30 cases), although this difference was not statistically significant ($P = .355$). However, in the last 5 years, there was a much more obvious trend that more thyroid cancer was found in MPHP cases (55.6%: 5/9 cases vs 16.7%, 3/18 cases, $P = .052$).

A total of 31 patients were followed up, with the average time of 38.16 ± 19.15 months, 2 cases of MPHP group recurred parathyroid hyperplasia confirmed by reoperation in the 8th and 11th year after the first operation.

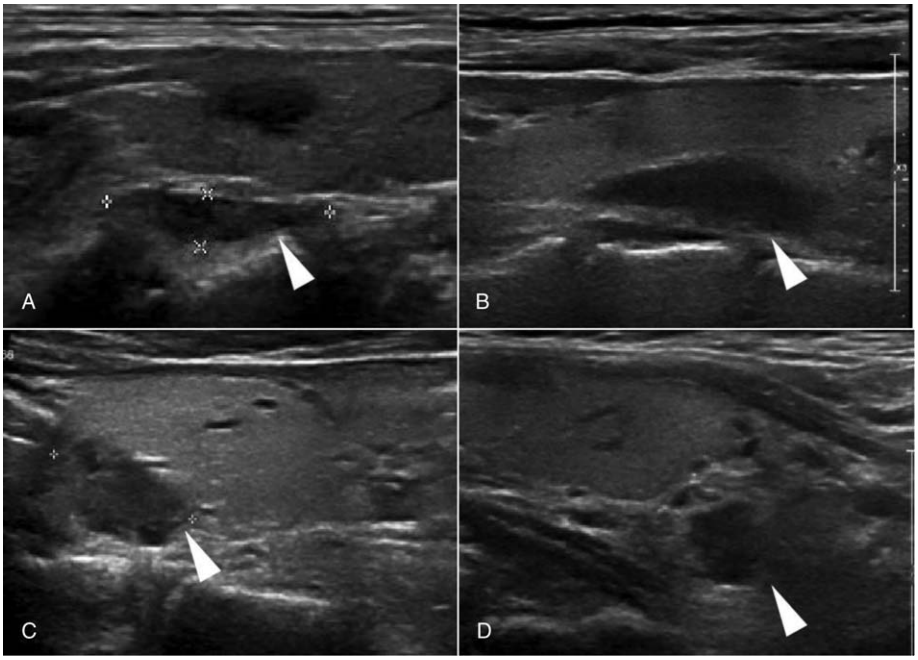

Figure 1. Arrows indicate the flat hyperplastic parathyroid glands of SPHP patients (A, B) and the round hyperplastic parathyroid glands in MPHP patients (C, D). MPHP = MEN1-associated PHP, SPHP = sporadic primary hyperparathyroidism.

Table 2

Ultrasonic characteristics of MPHP and SPHP patients.

	MPHP group N = 15	SPHP group N = 30	*P*
Parathyroid ultrasonic features	20/23 (92%)		
Round shape (long/short meridian < 2) (%)	20/23 (93%)	8/31 (25.8%)	**<.001**
Irregular shape (%)	20/23 (94%)	15/31 (48.4%)	.301
Vague boundary (%)	20/23 (95%)	0/31 (0%)	.13
Heterogeneous (%)	20/23 (96%)	14/31 (45.2%)	.218
Abundant blood flow (%)	19/20 (95%)	29/31 (93.5%)	.662
Thyroid ultrasonic features			
Irregular shape (%)	4/5 (80%)	7/7 (100%)	.417
Vague boundary (%)	2/5 (40%)	5/7 (71.4%)	.311
Orientation (%)	2/5 (40%)	2/7 (28.6%)	.576
Microcalcifications (%)	3/5 (60%)	6/7 (1.5%)	.364

MEN1 = multiple endocrine neoplasia type 1, MPHP = MEN1-associated PHP, SPHP = sporadic primary hyperparathyroidism.
Bold value represent significant difference.

4. Discussion

Consistent with our results, it has been reported that more than 98% of MEN1 patients have disease onset around the age of 50 years.[3] pHPT occurs in 90% of MEN1 patients.[17] In our study, MHPT patients presented with a very high parathyroid hormone level of 470.67 ± 490.74 pg/mL. Therefore, a substantial part of this population undergoes neck ultrasound to localize parathyroid diseases.[18] The accuracy of preoperative imaging is important because it is helpful for surgical planning and avoidance of unplanned conversion to extended bilateral neck exploration. Although normal parathyroid glands are not visible,[19] parathyroid gland enlargement allows visualization through ultrasound.[9,20] Indeed, studies have reported that this method had a sensitivity and specificity of 69% to 90% and 90% to 98%, respectively, for enlarged parathyroid gland localization.[21] High-resolution grayscale images, power Doppler ultrasound showing vascular flow imaging and examiner experience may increase the sensitivity of ultrasound. In our study, the overall preoperative detection rate of informal parathyroid glands by ultrasound was 91.2%. The thyroid and parathyroid glands are anatomically closely located and show an association in disease development. Because of the anatomical relationship between the thyroid and parathyroid glands, it is inevitable that the thyroid is imaged during neck ultrasound, which increases the chance of incidentally finding a thyroid tumor. In our study, 71.4% of cases were complicated by the presence of thyroid adenomatous nodules. The presence of adenomatous nodules might decrease the preoperative detection rate of parathyroid glands.[22,23] In the presence of highly enlarged parathyroid glands, it is difficult to make a preoperative distinction between enlarged parathyroid glands and adenomatous nodules; the missed enlarged parathyroid glands that were not detected preoperatively with ultrasound were relatively small, and none of them was detectable even when the preoperative imaging data were thoroughly reviewed retrospectively. Additionally, examiner knowledge and experience can be considered important contributors to the diagnostic utility of this method.[24]

In our study, a total of 51 parathyroid glands were surgically removed, with 20 and 31 glands in the MPHP and SPHP groups, respectively. More parathyroid lesions presented a round shape in the MPHP group than in the SPHP group (80.0% vs 25.8%, $P < .001$) by ultrasound. In the MPHP group, multiglandular parathyroid disease was much more frequent (40% vs 3.3%, $P = .003$), and more hyperplasia (46.7% vs 16.7%, $P = .039$) was found. It has been reported that the majority of pHPT cases (90%) occur sporadically. The most frequent cause of SHPT in more than 80% of patients is solitary adenoma, followed by hyperplasia in approximately 15% and cancer in 1% to 5%. The remaining 10% of cases occur as hereditary disorders, which include multiple endocrine neoplasia, familial hypocalciuric hypercalcemia, hyperparathyroidism jaw tumor and familial isolated pHPT.[25] Adenoma and hyperplasia are benign tumors, and the latter often involve 2 to 4 parathyroid glands, which also suggests that, when multiglandular parathyroid disease is found, hyperplasia will be considered first. For pHPT in MEN1 patients, some cases of parathyroid adenoma or hyperplasia have been reported,[26–28] while no studies have described the characteristics of parathyroid disease in detail until now. Our results are in line with previous studies showing that hyperplasia accounts for approximately 16.7% of SPHP patients. Regarding the MPHP patients, our study suggested that for the cause of HPT among MEN1 patients, 53.3% of cases had adenomas, and 46.7% of cases had hyperplasia. In addition, among 7 hyperplasia cases, 5 (71.4%) were multiglandular.

Despite considerable advancements in imaging techniques, distinguishing between different parathyroid lesions may occasionally be difficult.[9,19,20] It is difficult to distinguish parathyroid hyperplasia from adenoma by ultrasound, and studies are limited. Secrest and Grimes[29] evaluated the medical records of dogs with ultrasonographic examinations of their parathyroid glands and histologic diagnoses of parathyroid gland hyperplasia and adenoma and found no difference in lesion shape. In our study, we specifically studied the parathyroid disease of MPHP cohorts and found that the lesion shapes were different. We found that MPHP patients had more round parathyroid lesions than SPHP patients. A round shape and multiglandular features play an important role in the differential diagnosis of MPHP patients. Early diagnosis and treatment are helpful to prevent tumor metastasis and detect tumors early in other regions to carry out early intervention. It is also helpful to remind family members to screen for MEN1-related tumors. Regarding surgery, since parathyroid disease may occur in multiple parathyroid glands, open exploration is more appropriate than minimally invasive surgery.[3,30]

Since it is well known that thyroid nodules increase in prevalence with age,[31–33] the 2:1 age- and sex-matched study

design allowed a direct comparison of thyroid cancer rates in our study. In comparing the 2 cohorts, MPHP patients were not more likely to have histologic thyroid cancer (33.3% vs 23.3%, $P=.355$), although the sample size may have been underpowered for this parameter. However, the histologic thyroid cancer rate was higher in the MPHP group than in the SPHP group (55.6% vs 16.7%, $P=.052$) in the last 5 years. Considering that imaging tests, particularly the routine use of high-resolution ultrasound, differed over the course of the study period, the year of surgery was evaluated in relation to the extant type of parathyroid imaging. The median dates of thyroidectomy were November 2016 in the SPHP matched cohort and March 2014 in the MPHP cohort. Some thyroid nodules of previous cases could not be more fully evaluated before high-resolution ultrasound was added to the preoperative evaluation in prior years. This could also account for the higher detection rate of informal parathyroid glands by ultrasound in SPHP cases compared with MPHP cases (93.9% vs 87%, $P=.33$), although not significantly. There was no difference in the rate of indications for thyroidectomy and extent of surgery between the 2 groups. In both groups, unplanned thyroidectomy was 40%, and there was no difference according to the cohort. The difference in preoperative thyroid ultrasonic features between thyroid nodules in MPHP patients and those in SPHP patients was not significant.

The present study had some limitations. First, due to the rarity of MEN1 in the Chinese population, the sample size was limited. While the database is prospectively maintained, patients were treated according to standard practice at the time of surgery, which has evolved over time. Imaging resolution has also advanced, leading to the identification of more and smaller thyroid nodules than in prior years.[16,34] Thus, chronological bias may exist, as the rarity of MEN1 necessitates a long study period. In addition, thyroid ultrasound was not routinely employed in this population prior to 2005, and hence, small cancers may have been missed. Finally, while the matched design improves the ability to compare SPHP to MEN1 patients, matching also makes the results from the SPHP cohort less generalizable to all patients with SPHP, and because the matched groups are small, the results may suffer from type 2 error.

In conclusion, in our study, we found that multiglandular and round parathyroid disease are very important characteristics of MPHP patients. More concurrent thyroid cancer was found in MPHP patients in the last 5 years.

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