MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 4482-4489
DOI: 10.12659/MSM.898138

Received: 2016.02.21
Accepted: 2016.04.11
Published: 2016.11.21

Serum Calcium and Risk of Nonmedullary Thyroid Cancer in Patients with Primary Hyperparathyroidism

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Source of support: This study was supported by the National Natural Science Foundation of China (81170802 and 81400834) and Young Talents Training Project of Tongji University (2013KJ092)

Background: Clinical cases of nonmedullary thyroid carcinoma (NMTC) in combination with primary hyperparathyroidism (PHPT) have been reported occasionally. However, the clinical characteristics and risk factors of concomitant NMTC in PHPT patients remain unclear. This study aimed to assess the association between PHPT and NMTC, and evaluate the clinical characteristics and risk factors of NMTC in Chinese patients with PHPT.

Material/Methods: This was a retrospective cohort analysis. We reviewed the medical records of 155 patients who underwent surgery for PHPT in two large medical centers in China between 2009 and 2014. The clinical manifestations, biochemical abnormalities, and histological characteristics of PHPT patients were analyzed.

Results: Of the 155 patients with PHPT, 58 patients (37.4%) had thyroid nodules and 12 patients (7.7%) were ill with concomitant NMTC. PHPT patients with NMTC demonstrated significantly lower preoperative serum calcium levels compared to PHPT patients with benign thyroid nodules ($p<0.05$). A significantly negative association between preoperative serum calcium levels and the presence of NMTC was found in PHPT patients ($p<0.05$). Furthermore, ROC analysis revealed that albumin-corrected serum calcium levels <2.67 mmol/L had good capacity to differentiate the PHPT patients with NMTC from those with benign thyroid nodules.

Conclusions: Compared with the reported much lower prevalence of thyroid carcinoma in the general population, our results suggest that PHPT might be a risk factor for the malignancy of thyroid nodules; a lower level of serum calcium may predict the existence of NMTC in PHPT patients with thyroid nodules.

MeSH Keywords: **Hyperparathyroidism, Primary • Parathyroidectomy • Thyroid Neoplasms • Thyroid Nodule**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/898138

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Background

Hyperparathyroidism (HPT) is one of the important endocrine disorders, which includes primary hyperparathyroidism (PHPT), secondary hyperparathyroidism (SHPT) and tertiary hyperparathyroidism (THPT). PHPT is present in up to 0.04–0.1% of the general population, with a peak during the 5th and 6th decades of life [1,2]. Parathyroid adenoma occurs in 75–85%of PHPT patients. Symptomatic patients and select asymptomatic patients that meet the guidelines of the 2008 International Workshop on Asymptomatic Primary Hyperparathyroidism [3] are candidates for parathyroid surgery. It has been reported that 15–75% of PHPT patients have coexisting thyroid diseases, among whom the prevalence of nonmedullary thyroid carcinoma (NMTC) associated with PHPT has been reported as between 2–18% [1,2,4–9]. However, it is still controversial whether the concomitance of PHPT and NMTC is coincidental or due to common pathogenic factors, including head and neck irradiation [7], genetic factors, or other unknown factors.

Previous reports consist mostly of case reports and small case series outside China. It is not known whether Chinese patients with NMTC in combination with PHPT have similar or different features. Therefore, in order to explore the prevalence and risk factors of NMTC concomitant with PHPT in the Chinese population, the medical records of 155 patients who underwent surgery for PHPT in two large medical centers between 2009 and 2014 were reviewed and analyzed.

Material and Methods

Patients

The protocol and procedures employed were reviewed and approved by the Ethic Committees of our hospital (2009-01-0H). We collected the clinical data of 155 patients with PHPT who received surgery in two large medical centers (Shanghai Tongji Hospital and the First Affiliated Hospital of Nanjing Medical University) between January 2009 and December 2014. The patients had a mean age of 55±14 years (range: 18–79 years), consisting of 38 males and 117 females. With confirmed PHPT based upon medical history, physical examination, and standard diagnostic laboratory criteria, patients were eligible for inclusion. Patients who underwent prior thyroid or parathyroid surgery, those with medullary thyroid carcinoma (MTC), those with multiple endocrine neoplasia (MEN) or familial HPT, and those with secondary HPT or tertiary HPT were excluded from this study.

Methods

The following data were collected in PHPT patients: age at time of operation, gender, personal history, family history, clinical manifestations including nephrolithiasis, bone pain, gastrointestinal symptoms and neuropsychiatric symptoms, physical examinations, preoperative blood biochemical tests, preoperative neck high-resolution ultrasound, parathyroid technetium-99m-sestamibi (^{99m}Tc MIBI) imaging, operation records, and postoperative histology. All patients underwent preoperative neck high-resolution ultrasound and were defined as having thyroid nodules if they had one or more nodules on preoperative ultrasound. PHPT patients with thyroid nodules received intensive intraoperative thyroid exploration. Blood biochemical tests included serum immunoreactive intact PTH level (reference range, 15–65 pg/mL, Roche kit), total serum calcium (2.2–2.65 mmol/L), phosphorus (0.81–1.45 mmol/L), creatinine (Cr, 44–133 umol/L), blood uric nitrogen (BUN, 2.9–8.2 mmol/L), albumin (40–55 g/L), total serum alkaline phosphatase (AKP, 30–120 U/L), serum thyroglobulin antibody (TgAb, <115 IU/mL), thyroid stimulating hormone (TSH, 0.27–4.2 mIU/L), fasting blood glucose (FBG, 3.9–6.1 mmol/L), triglyceride (TG, 0–1.7 mmol/L), total cholesterol (TC, 3.1–5.2 mmol/L), high density lipoprotein cholesterol (HDL-C, >0.91 mmol/L) and low density lipoprotein cholesterol (LDL-C, <3.12 mmol/L). The albumin-corrected serum calcium level (mmol/L) was calculated using the following formula: [40 g/L-serum albumin concentration (g/L)] ×0.02 + measured total serum calcium (mmol/L). Serum calcium and serum PTH concentrations were measured at least twice during diagnosing. Histopathological diagnosis for PHPT and NMTC were completed by two experienced pathologists independently and recorded as the final diagnoses.

Statistical analyses

All statistical analyses were performed using SPSS (version 18.0; SPSS Inc, Chicago, Illinois, USA). All continuous variables were presented as mean ±SD, except for data that did not have a normal distribution, which were expressed as medians (interquartile ranges). All categorical variables were presented as proportions. Comparisons of the means and proportions were performed with independent samples *t*-test and the chi-square test. Risk factors associated with the presence of NMTC in PHPT patients were determined using the Spearman rank correlation analyses. To investigate the associations between NMTC and PHPT, the unadjusted and multivariate adjusted logistic regression analyses were used to assess odds ratios (OR) and the corresponding 95% confidence intervals (CI). A receiver operating characteristic (ROC) analysis was conducted to determine the capacity of the clinical and biochemistry markers to predict NMTC in PHPT patients with thyroid nodules. Differences were considered significant if $p<0.05$.

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Table 1. Association of thyroid nodule and parathyroid pathology in patients with PHPT.

	Not concomitant with thyroid nodule	Concomitant with thyroid nodule	
		Benign	Malignant
Parathyroid hyperplasia	20	7	4
Parathyroid adenoma	76	37	8
Parathyroid carcinoma	1	2	0
Total	97	46	12

PHPT – primary hyperparathyroidism.

Results

Clinical characteristics of PHPT patients

In the 155 cases of PHPT patients, the preoperative serum PTH level was 268.6 pg/mL (165.7–538.5 pg/mL). The serum creatinine level was 72.8±34.7 μmol/L (range: 26.1–214.9 μmol/L). In the preoperative ultrasound examination, thyroid nodules were detected in 37.4% (58/155) of patients, and 7.7% (12/155) had malignant thyroid cancers. The malignant rate of thyroid nodules in PHPT patients was 20.7% (12/58).

Parathyroid histology is shown in Table 1: 1) 20% (31/155) were reported to have parathyroid hyperplasia; among these, 7.1% (11/155) had thyroid nodules and 2.6% (4/155) had concomitant NMTC. The malignancy rate of thyroid nodules in patients with parathyroid hyperplasia was 36.4% (4/11). 2) 78.1% (121/155) of patients were reported to have parathyroid adenoma; among these, 29% (45/155) had thyroid nodules and 5.2% (8/155) had concomitant NMTC. The malignant rate of thyroid nodules in patients with parathyroid adenoma was 17.8% (8/45). 3) Only 1.9% (3/155) of patients were reported to have parathyroid carcinoma; two of the three cases were combined with thyroid nodules and no patients were combined with concomitant NMTC. We found no significant difference in the malignancy rate of thyroid nodules between patients with parathyroid hyperplasia and patients with parathyroid adenoma.

Analysis of the risk factors for thyroid nodules in PHPT patients

The 58 PHPT patients with thyroid nodules had a mean age of 48±14 years (range: 18–79 years), consisted of 14 males and 44 females, and included 28 patients with a single thyroid nodule and 30 patients with multiple thyroid nodules. In patients with a single thyroid nodule, 14.3% (4/28) were identified as having concomitant NMTC, whereas in patients with multiple thyroid nodules, 26.7% (8/30) had concomitant NMTC. The malignancy rate of single thyroid nodules in PHPT patients was not different from the malignancy rate of multiple thyroid nodules in PHPT patients ($p>0.05$).

To analyze the risk factors for thyroid nodules in PHPT patients, the following data were compared between the two subgroups that included 58 patients with thyroid nodules and 97 patients without thyroid nodules, according to the preoperative neck high-resolution ultrasound: age at the time of operation, gender, personal history of cancers, diabetes, hypertension and coronary artery disease, preoperative serum calcium, serum phosphorus, AKP, serum PTH, TSH, TgAb, FBG, and blood lipid levels (Table 2).The age of patients without thyroid nodules was 58±12 years, which was significantly older than that of PHPT patients with thyroid nodules ($p<0.001$), whereas no significant difference in gender distribution, personal histories, and preoperative blood parameters could be detected between these two groups.

Clinical characteristics of PHPT patients in combination with NMTC

The 12 PHPT patients with concomitant NMTC had a mean age of 55±18 years (range: 18–79 years), and consisted of 4 males and 8 females. Their preoperative serum PTH level was 268.6 pg/mL (165.7–538.5 pg/mL), and the mean creatinine level was 67.5±19.1 μmol/L (range: 36.5–90.1 μmol/L). Postoperative histology of these 12 patients proved that 8 patients had parathyroid adenoma (single adenoma) and 4 patients had parathyroid hyperplasia, including 1 case of retrosternal parathyroid hyperplasia. The pathological types of the 12 NMTCs in PHPT patients were all papillary carcinomas; 58.3% (7/12) were micropapillary carcinomas (with greatest dimension ≤1 cm), 8.3% (1/12) were multifocal, and 8.3% (1/12) had metastasis to lymph node (Table 3).

Analysis of the risk factors for NMTC in PHPT patients

To analyze the risk factors of NMTC in PHPT patients, the clinical and biochemical data were compared between PHPT patients with and without NMTC (Table 4). Compared with PHPT patients without NMTC, patients with NMTC demonstrated significantly lower preoperative total serum calcium and albumin-corrected serum calcium levels ($p<0.05$). All the other parameters were not different between the two subgroups.

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Table 2. The clinical and biochemical features in PHPT patients with and without thyroid nodules.

	Total PHPT (N=155)	With thyroid nodule (N=58)	Without thyroid nodule (N=97)
Age (years)	55±14	48±14	58±12*
Gender			
Male	38 (24.5%)	14 (24.1%)	24 (24.7%)
Female	117 (75.5%)	44 (75.9%)	73 (75.3%)
Comorbidity			
Hypertension	39 (25.2%)	17 (29.3%)	22 (22.7%)
Diabetes	14 (9.0%)	3 (5.2%)	11 (11.3%)
Coronary heart disease	7 (4.5%)	4 (6.9%)	3 (3.1%)
Malignant tumor history	9 (5.8%)	4 (6.9%)	5 (5.2%)
Serum calcium (mmol/L)	2.96±0.41	2.94±0.39	2.98±0.42
Albumin-corrected serum calcium level (mmol/L)	2.90±0.42	2.83±0.33	2.95±0.47
Serum phosphorus (mmol/L)	0.88±0.42	0.84±0.19	0.90±0.51
AKP (U/L)	140.2 (92.0–235.1)	144.8 (88.6–176.3)	138.9 (92.3–239.5)
PTH (pg/mL)	268.6 (165.7–538.5)	224.4 (157.0–439.6)	297.4 (176.3–600.8)
FBG (mmol/L)	5.3±0.9	5.2±0.7	5.4±1.0
TG (mmol/L)	1.71±1.14	1.65±0.96	1.74±1.25
TC (mmol/L)	4.97±0.89	5.0±0.99	4.95±0.84
HDL-C (mmol/L)	1.26±0.36	1.31±0.36	1.23±0.35
LDL-C (mmol/L)	3.16±0.72	3.15±0.70	3.17±0.74
Cr (μmol/L)	72.8±34.7	72,2±30.6	73.2±37.0
BUN (mmol/L)	5.56±2.40	5.93±2.67	5.36±2.24
TSH (mIU/L)	1.97 (1.32–3.43)	1.75 (1.14–3.87)	2.0 (1.45–3.11)
TgAb (IU/mL)	22.5 (14.5–95.0)	20.4 (12.8–54.6)	28.1 (16.8–181.8)

NS – not significant. * With thyroid nodule *vs.* without thyroid nodule, $p<0.001$.

Furthermore, we divided the 58 PHPT patients with thyroid nodules into two subgroups, i.e., a malignant thyroid nodule subgroup including 12 patients with NMTC, and a benign thyroid nodule subgroup including 46 patients with benign thyroid nodules, according to the patient's pathological report on thyroid tissue after surgery. The data comparing the two subgroups are shown in Table 4. Compared with the benign thyroid nodule subgroup, patients with NMTC demonstrated significantly lower preoperative total serum calcium and albumin-corrected serum calcium levels ($p<0.05$). Higher serum phosphorus levels were also observed in NMTC patients ($p<0.05$). Interestingly, preoperative serum PTH levels were not statistically different between the two subgroups. All the other parameters were also not different between the two subgroups. A significant negative association between the preoperative albumin-corrected serum calcium levels and the presence of NMTC was found in PHPT patients with thyroid nodules using Spearman rank correlation analyses (Spearman $r=-0.405$; $p=0.019$). To further investigate the associations between NMTC and PHPT, unadjusted and multivariate adjusted logistic regression analyses were used. The presence of NMTC was significantly associated with decreased levels of albumin-corrected serum calcium (OR: 0.023; 95% CI: 0.001–0.624; $p=0.025$). Further adjustment for age and sex (model 1) did not materially change the association (OR: 0.021; 95% CI: 0.001–0.706; $p=0.031$).The ROC analysis revealed that albumin-corrected serum calcium levels

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Table 3. Characteristics of thyroid Carcinoma in patients with PHPT.

Case	Age	Sex	Location of tumor	Number of tumors	Tumor type	Tumor size (cm)	Lymph node metastasis
1	62	F	Left lobe	1	Micropapillary carcinoma	0.2	No
2	43	M	Left lobe	1	Papillary carcinoma	1.2×0.6×0.5	No
3	75	F	Right lobe	1	Micropapillary carcinoma	0.3	No
4	64	F	Right lobe	1	Micropapillary carcinoma	0.3	No
5	41	F	Right lobe	1	Micropapillary carcinoma	0.3	No
6	47	F	Left lobe, right lobe	2	Papillary carcinomas	2, 1	No
7	61	F	Right lobe	1	Papillary carcinoma	1	No
8	79	M	Left lobe	1	Papillary carcinoma	3×2	No
9	50	F	Left lobe	1	Micropapillary carcinoma	0.7	No
10	73	M	Right lobe	1	Micropapillary carcinoma	0.9	No
11	45	F	Left lobe	1	Micropapillary carcinoma	0.5	No
12	18	M	Right lobe	1	Papillary carcinoma	1.7	Yes (1/2)

<2.67 mmol/L had good capacity to differentiate the PHPT patients with NMTC from those with benign thyroid nodules, with an area under the curve (AUC) of 0.748 (p=0.022). This cut-off point for albumin-corrected serum calcium level had a sensitivity of 63.6%, and a specificity of 77.3% for predicting NMTC in PHPT patient with thyroid nodules.

Discussion

The thyroid gland and parathyroid gland are adjacent endocrine organs. Thyroid disease concomitant with parathyroid disease has been reported previously, the prevalence of NMTC in patients with PHPT ranged from 2–18%, which corresponded to the prevalence of 7.7% in this study. The characteristics of thyroid cancers associated with PHPT from previous literature are summarized in Table 5. The majority of previous studies were done in the United States and Europe; a similar study in the Chinese population has not been reported as of yet. Previous statistical data showed that the prevalence of thyroid cancer in the general population ranges from 0.5–10 per 10,000 [6,10], which was significantly lower than that in our PHPT patients. Our results also showed an overall 20.7% malignancy rate of thyroid nodules in PHPT patients, which seemed higher than the rate of malignancy (5–15%) in general patients with thyroid nodules [11]. From available data, we speculate that PHPT might be a pathogenic factor or at least a risk factor for malignancy of thyroid nodules. The high concurrence of these two disorders in the same patients might not be coincidental; some specific factors, such as environmental factors, genetic factors, or some other unknown factors, might connect NMTC with PHPT.

Recently, several studies have reported on possible risk factors for the coexistence of NMTC and PHPT. Earlier findings suggested that a history of head and neck irradiation, mostly during adolescence and childhood, is a pathogenic factor for the development of associated NMTC in PHPT patients. However, this factor was not present in our study, because none of the 12 patients with NMTC had had prior radiation of the head and neck. High PTH levels have been reported to affect phagocytosis, T-cell sensitivity, and B-cell function, thus accounting for the immune dysfunction of patients and increased incidence of cancers [12,13]. Several studies indicated that HPT was associated with the development of urinary tract cancer and breast cancer, as well as thyroid cancer [14,15]. However, no connection between PTH level and the presence of NMTC was found in our PHPT patients, and no statistical difference in preoperative serum PTH levels was detected between PHPT patients with NMTC and PHPT patients with benign thyroid nodules. It was remarkable that PHPT patients with NMTC demonstrated significantly lower preoperative albumin-corrected serum calcium levels compared with PHPT patients with benign thyroid nodules. A significant negative association between preoperative albumin-corrected serum calcium levels and the presence of NMTC was found in PHPT patients with thyroid nodules using the Spearman rank correlation analysis and logistic regression analysis. Based on our results, a lower level of serum calcium might be a risk factor for NMTC in PHPT patients with thyroid nodules. There have

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Table 4. The clinical and biochemical features between PHPT Patients with and without NMTC, PHPT patients with benign and malignant thyroid nodules.

	Without NMTC (N=143)	Benign thyroid nodule (N=46)	NMTC (N=12)
Age (years)	54±13	46±12	55±18
Gender			
Male	34 (23.8%)	10 (21.7%)	4 (33.3%)
Female	109 (76.2%)	36 (78.3%)	8 (66.7%)
Comorbidity			
Hypertension	34 (23.8%)	12 (26.1%)	5 (41.7%)
Diabetes	14 (9.8%)	3 (6.5%)	0
Coronary heart disease	7 (4.9%)	4 (8.7%)	0
Malignant tumor history	9 (6.3%)	4 (8.7%)	0
Serum calcium (mmol/L)	2.98±0.41	3.00±0.40	2.74±0.26*,#
Albumin-corrected serum calcium level (mmol/L)	2.94±0.43	2.92±0.32	2.63±0.26*,#
Serum phosphorus (mmol/L)	0.87±0.43	0.8±0.16	0.93±0.22#
AKP (U/L)	146.4 (93.7–235.5)	150.3 (105.5–198.2)	107.3 (83.0–172.5)
PTH (pg/mL)	295.1 (171.0–565.0)	243.3 (167.7–492.2)	165.5 (124.6–312.3)
FBG (mmol/L)	5.3±0.9	5.1±0.7	5.3±0.6
TG (mmol/L)	1.70±1.17	1.59±0.96	1.75±1.01
TC (mmol/L)	4.92±0.84	4.81±0.86	5.28±1.14
HDL-C (mmol/L)	1.25±0.36	1.33±0.39	1.27±0.33
LDL-C (mmol/L)	3.13±0.71	3.04±0.64	3.31±0.79
Cr (μmol/L)	73.6±36.3	74.6±35.2	67.5±19.1
BUN (mmol/L)	5.5±2.4	5.7±2.7	6.2±2.7
TSH (mIU/L)	1.93 (1.37–3.22)	1.75 (1.11–3.70)	2.20 (1.14–5.48)
TgAb (IU/mL)	23.9 (14.7–151.0)	21.8 (14.6–147.3)	15.5 (10.1–42.0)

NS – not significant. * Without NMTC *vs.* NMTC, $p<0.05$. # Benign thyroid nodule *vs.* NMTC, $p<0.05$.

been several published reports on the association between serum calcium level and various cancers, as described in the following examples. 1) The total serum calcium, and ionized and albumin-corrected calcium concentrations of patients with colorectal cancer were significantly lower than those of controls [16]. Serum calcium levels were inversely correlated with blood CA19-9 concentration, which could support the significance of serum calcium not only as a pathogenic factor but also as a prognostic factor in the development of colorectal cancer [16]. 2) Another study demonstrated a highly significant negative association of cancer and serum calcium levels in women [17]. 3) A positive link between serum calcium, esophageal cancer, and colorectal cancer in women was found in a prospective study [18]. 4) For prostate cancer, there were two large Swedish studies. The AMORIS study, with 6,353 incident cases, showed a weak negative association between serum calcium levels and prostate cancer [19], whereas in the Malmø Preventive Project, this association was only seen in young overweight men [20]. 5) For breast cancer, there was an inverse connection with serum calcium [21], as well as no association with serum calcium. 6) HPT was also associated with the development of colon cancer [22] as well as gastric carcinoma [23]. To date, the correlation between thyroid cancer and serum calcium level remains unclear. In our study, we

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Table 5. The prevalence of thyroid carcinoma in patients with primary hyperparathyroidism: comparison of the data from literature with that from the present study.

Study	No. of PHPT patients	Thyroid cancer n (%)	PTC n (%)	FTC n (%)	MTC n (%)	Country
Bentrem DJ (2002)	580	12/580 (2.1)	12/580 (2.1)	0	0	USA
Kösem M (2004)	51	9/51 (17.6)	9/51 (17.6)	0	0	Turkey
Ogawa T (2007)	85	9/85 (10.6)	7/85 (8.2)	1/85 (1.2)	0	Japan
Morita SY (2008)	200	12/200 (6.0)	12/200 (6)	0	0	USA
Wilson SD (2011)	916	41/916 (4.4)	36/916 (3.9)	5/916 (0.5)	0	USA
Arciero CA (2012)	94	6/94 (6.4)	5/94 (5.3)	1/94 (1.1)	0	USA
Onkendi EO (2012)	470	79/470 (16.8)	75/470 (16)	0	5/470 (1.1)*	USA
Lehwald N (2013)	1464	41/1464 (2.8)	35/1464 (2.4)	6/1464 (0.4)	0	Germany
Xue Y (in this study)	155	12/155 (7.7)	12/155 (7.7)	0	0	China

* Indicates one patient who had both MTC and PTC; PTC – papillary thyroid carcinoma; FTC – follicular thyroid carcinoma; MTC – medullary thyroid cancer; NA – no data available.

first found that serum calcium levels were inversely associated with the existence of NMTC in PHPT patients. However, the underlying pathophysiological mechanism of our clinical findings requires further investigation.

In addition to the above factors, the genetic link between PHPT and NMTC needs to be elucidated. Genetic syndromes account for approximately 5–15% of all cases of PHPT [24]. The most common hereditary syndromes associated with PHPT are MEN1 and MEN-2a [25], neonatal severe hyperparathyroidism (NSHPT), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and familial isolated hyperparathyroidism (FIHP). However, the association between the aforementioned genetic PHPT and NMTC remains unclear. MTC associated with PHPT is one of the main characteristics in MEN-2a patients [26,27]. RET mutations are the only recognized genetic associations with MEN2 and familial MTC that follow a classic familial inheritance pattern [28]. To date, the genetic relationship between NMTC (including thyroid papillary carcinoma, follicular carcinoma, and undifferentiated carcinoma) and PHPT is not well defined.

The modern operative approach for PHPT has transitioned from traditional bilateral neck exploration to a more focal approach with minimally invasive access, which depends on ^{99m}Tc MIBI imaging in locating parathyroid adenomas and intraoperative PTH monitoring to document the normalization of PTH levels [1,29]. However, the minimally invasive approach can provide inadequate anatomic information of the thyroid gland and lead to missing synchronous thyroid abnormalities [4,30]. In that situation, a substantial preoperative thyroid assessment has been recommended, including physical examination, ultrasound and CT scans of the neck, and FNA. Prinz et al. noted that only in 37% of patients with concurrent disease was a thyroid nodule palpated preoperatively. Thus, we believe that a preoperative ultrasound of the thyroid gland may be more beneficial than thyroid palpation to locate parathyroid adenomas and detect concomitant thyroid nodules in PHPT patients [1,4]. Furthermore, our data showed that in PHPT patients, the prevalence of thyroid microcarcinoma and the prevalence of thyroid carcinoma with greatest dimension >1 cm were very similar (7/155 *vs.* 5/155); therefore, PHPT patients with thyroid nodules on preoperative ultrasonography, regardless of the size of the detected nodule, should be recommended for intensive intraoperative thyroid exploration.

There were some limitations in this study. We documented an inverse association between NMTC and serum calcium values in patients with PHPT, but pathophysiological mechanisms underlying this association remained unknown. The majority of our patients came from Jiangsu province and Shanghai city, which are both located in the eastern part of China; therefore, our results may not be extrapolatable to the patients of China in general.

Conclusions

Our results revealed that PHPT might be a risk factor for the malignancy of thyroid nodules, and that a level of albumin-corrected serum calcium less than 2.67 mmol/L had good capacity to predict NMTC in PHPT patients with thyroid nodules. As bilateral neck exploration for surgical treatment of PHPT has been replaced by a minimally invasive approach, intensive preoperative and intraoperative thyroid exploration might be necessary to identify concomitant thyroid cancers.

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References:

1. Arciero CA, Shiue ZS, Gates JD et al: Preoperative thyroid ultrasound is indicated in patients undergoing parathyroidectomy for primary hyperparathyroidism. J Cancer, 2012; 3: 1–6
2. Morita SY, Somervell H, Umbricht CB et al: Evaluation for concomitant thyroid nodules and primary hyperparathyroidism in patients undergoing parathyroidectomy or thyroidectomy. Surgery, 2008;144: 862–66; discussion 866–68
3. Bilezikian JP, Khan AA, Potts JT, Jr., Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab, 2009; 94: 335–39
4. Bentrem DJ, Angelos P, Talamonti MS, Nayar R: Is preoperative investigation of the thyroid justified in patients undergoing parathyroidectomy for hyperparathyroidism? Thyroid, 2002; 12: 1109–12
5. Kosem M, Algun E, Kotan C et al: Coexistent thyroid pathologies and high rate of papillary cancer in patients with primary hyperparathyroidism: Controversies about minimal invasive parathyroid surgery. Acta Chir Belg, 2004; 104: 568–71
6. Ogawa T, Kammori M, Tsuji E et al: Preoperative evaluation of thyroid pathology in patients with primary hyperparathyroidism. Thyroid, 2007; 17: 59–62
7. Wilson SD, Doffek KM, Wang TS et al: Primary hyperparathyroidism with a history of head and neck irradiation: The consequences of associated thyroid tumors. Surgery, 2011; 150: 869–77
8. Onkendi EO, Richards ML, Thompson GB et al: Thyroid cancer detection with dual-isotope parathyroid scintigraphy in primary hyperparathyroidism. Ann Surg Oncol, 2012; 19: 1446–52
9. Lehwald N, Cupisti K, Krausch M et al: Coincidence of primary hyperparathyroidism and nonmedullary thyroid carcinoma. Horm Metab Res, 2013; 45: 660–63
10. Jemal A, Tiwari RC, Murray T et al: Cancer statistics, 2004. Cancer J Clin, 2004; 54: 8–29
11. Brito JP, Gionfriddo MR, Al Nofal A et al: The accuracy of thyroid nodule ultrasound to predict thyroid cancer: Systematic review and meta-analysis. J Clin Endocrinol Metab, 2014; 99: 1253–63
12. Geara AS, Castellanos MR, Bassil C et al: Effects of parathyroid hormone on immune function. Clin Dev Immunol, 2010; 2010: pii: 418695
13. Tzanno-Martins C, Futata E, Jorgetti V, Duarte AJ: Immune response in hemodialysis patients: Is there any difference when low and high iPTH levels are compared? Clin Nephrol, 2000; 54: 22–29
14. Pickard AL, Gridley G, Mellemkjae L et al: Hyperparathyroidism and subsequent cancer risk in Denmark. Cancer, 2002; 95: 1611–17
15. Michels KB, Xue F, Brandt L, Ekbom A: Hyperparathyroidism and subsequent incidence of breast cancer. Int J Cancer, 2004; 110: 449–51
16. Fuszek P, Lakatos P, Tabak A et al: Relationship between serum calcium and CA 19-9 levels in colorectal cancer. World J Gastroenterol, 2004; 10: 1890–92
17. Jorde R, Schirmer H, Njolstad I et al: Serum calcium and the calcium-sensing receptor polymorphism rs17251221 in relation to coronary heart disease, type 2 diabetes, cancer and mortality: The Tromso Study. Eur J Epidemiol, 2013; 28: 569–78
18. Wulaningsih W, Michaelsson K, Garmo H et al: Serum calcium and risk of gastrointestinal cancer in the Swedish AMORIS study. BMC Public Health, 2013; 13: 663
19. Van Hemelrijck M, Hermans R, Michaelsson K et al: Serum calcium and incident and fatal prostate cancer in the Swedish AMORIS study. Cancer Causes Control, 2012; 23: 1349–58
20. Halthur C, Johansson AL, Almquist M et al: Serum calcium and the risk of prostate cancer. Cancer Causes Control, 2009; 20: 1205–14
21. Almquist M, Manjer J, Bondeson L, Bondeson AG: Serum calcium and breast cancer risk: Results from a prospective cohort study of 7,847 women. Cancer Causes Control, 2007; 18: 595–602
22. Isik A, Peker K, Firat D et al: Importance of metastatic lymph node ratio in non-metastatic, lymph node-invaded colon cancer: A clinical trial. Med Sci Monit, 2014; 20: 1369–75
23. Isik A, Okan I, Firat D et al: A new prognostic strategy for gastric carcinoma: Albumin level and metastatic lymph node ratio. Minerva Chir, 2014; 69: 147–53
24. Roizen J, Levine MA: Primary hyperparathyroidism in children and adolescents. J Chin Med Assoc, 2012; 75: 425–34
25. Pallan S, Rahman MO, Khan AA: Diagnosis and management of primary hyperparathyroidism. BMJ, 2012; 344: e1013
26. Lodish M: Multiple endocrine neoplasia type 2. Front Horm Res, 2013; 41: 16–29
27. Jesic MD, Tancic-Gajic M, Jesic MM et al: Prophylactic thyroidectomy for asymptomatic 3-year-old boy with positive multiple endocrine neoplasia type 2A mutation (codon 634). Srp Arh Celok Lek, 2014; 142: 72–74
28. Elisei R, Romei C, Cosci B et al: RET genetic screening in patients with medullary thyroid cancer and their relatives: experience with 807 individuals at one center. J Clin Endocrinol Metab, 2007; 92: 4725–29
29. Bishop B, Wang B, Parikh PP, Lew JI: Intraoperative parathormone monitoring mitigates age-related variability in targeted parathyroidectomy for patients with primary hyperparathyroidism. Ann Surg Oncol, 2015; 22(Suppl.3): 655–61
30. Gracie D, Hussain SS: Use of minimally invasive parathyroidectomy techniques in sporadic primary hyperparathyroidism: Systematic review. J Laryngol Otol, 2012; 126: 221–27

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