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ORIGINAL ARTICLE

Can Biochemical Markers and Ultrasonographical Diameters Be Used to Predict Histopathological Diagnosis in Patients with Primary Hyperparathyroidism?

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Abstract
We aimed to determine whether any biochemical feature or ultrasonographical diameter can help to predict histopathological diagnosis in patients with primary hyperparathyroidism (PHPT). Data of 398 patients operated for PHPT were evaluated. Patients were grouped as parathyroid hyperplasia (PH), parathyroid adenoma (PA), parathyroid carcinoma (PC) + atypical, and parathyroid adenoma (APA) histopathologically. Three-way ROC analysis was used to evaluate the performance of variables to determine the three groups. The volume under surface (VUS) > 0.17 was giving information beyond chance. Cut-off levels and correct classification rates were calculated when the VUS value was significantly > 0.17. There were 20 patients with PH, 343 with PA, and 35 with PC + APA (30 APA, 5 PC). Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone were significantly different between groups ($p = 0.007$, $p = 0.003$, $p = 0.035$, and $p < 0.001$, respectively). Ultrasonographically, there were significant differences in the anteroposterior, transverse, and longitudinal diameters of lesions ($p = 0.001$, $p = 0.001$, and $p = 0.002$, respectively). The VUS values of serum calcium and anteroposterior and longitudinal diameters of lesions were statistically significantly higher than 0.17. Serum calcium lower than 10.73 mg/dL, 10.73–11.45 mg/dL, and > 11.45 mg/dL were predictive for PH, PA, and PC + APA, respectively. Ultrasonographically, anteroposterior diameter < 6.0 mm and longitudinal diameter < 14.0 mm were predictive for PH, and anteroposterior diameter of > 12.9 mm and longitudinal diameter of > 22.2 mm were predictive for PC + APA. Values in between were predictive for PA. In this study, we found that serum calcium levels and anteroposterior and longitudinal diameters of lesion in ultrasonography can predict the histopathological diagnosis in patients with PHPT.

Keywords Parathyroid adenoma · Parathyroid hyperplasia · Atypical parathyroid adenoma · Parathyroid carcinoma

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease after diabetes and thyroid diseases. It is characterized by excessive and uncontrolled secretion of parathyroid hormone (PTH) [1]. The cause is parathyroid adenoma (PA) in approximately 90%, parathyroid hyperplasia (PH) in 10%, and parathyroid carcinoma (PC) in less than 1% of the patients [2, 3].

While PA is suggested to be a monoclonal lesion, PH is considered to be an oligo- or poly-clonal lesion [4, 5]. Histopathologically, PC is characterized by mitoses, atypia/pleomorphism, and/or a trabeculated or sheet-like growth pattern. There is also lymphovascular invasion and/or invasion into soft tissue, thyroid parenchyma, or muscle. When there are some cytological features of a PC but there is no histopathological evidence of invasion, the histopathological diagnosis is an atypical parathyroid adenoma (APA) [6, 7]. Surgery is the main treatment of PHPT; however, the surgical approach might differ according to the etiology. In patients with a single PA, a minimally invasive

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parathyroidectomy is the preferred surgical approach, while subtotal parathyroidectomy or total parathyroidectomy with parathyroid autotransplantation is performed in PH. The current definitive treatment of PC is en-bloc resection of the tumor with any involved structures, which avoids rupture and spillage of the tumor. If clinical suspicion of PC can be made prior to surgery, early diagnosis and a radical therapy can be implemented.

Preoperative discrimination of these different parathyroid lesions may sometimes be difficult due to similar or overlapping clinical symptoms and biochemical findings [8, 9]. However, it is important to predict the histopathological result of the lesion preoperatively to avoid insufficient or aggressive treatment approaches. In this case series analysis, we aimed to determine whether any preoperative biochemical marker or any ultrasonography (US) feature can be used to predict different histopathological lesions in patients with PHPT.

Patients and Methods

Patients

The data of 420 patients operated for PHPT between January 2010 and September 2018 in our center were reviewed. The diagnosis of PHPT was made by hypercalcemia and PTH levels that are inappropriately high for the hypercalcemic state. Other PTH-dependent causes of hypercalcemia (thiazide diuretics or lithium use, familial hypocalciuric hypercalcemia) were excluded. Normocalcemic PHPT patients and one patient with MEN-1 syndrome were excluded as well. Eventually, 398 patients were included in the analysis. Patients presenting with pathological fractures, osteitis fibrosa cystica, nephrolithiasis, nephrocalcinosis, impaired renal functions, or some non-specific symptoms such as depression, lethargy, and bone pain were considered to be symptomatic. Patients who do not have obvious signs and symptoms that may be related with increased Ca or PTH were considered to have asymptomatic PHPT [10]. Operation indications in patients with asymptomatic PHPT are defined in a series of guidelines which were lastly updated in 2014 by the "Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism [11]." We suggested operation in such patients according to the recommendations published in 2009 and 2014 [11, 12].

Laboratory Examinations

Preoperative serum Ca, albumin, phosphorus (P), intact PTH (iPTH), alkaline phosphatase (ALP), 25-hydroxyvitamin D, creatinine (Cr) and 24-h urinary Ca (uCa), and P (uP) were obtained from the medical records. Serum Ca was measured using a reference clinical chemistry laboratory (8.5–10.5 mg/dL) (Roche Diagnostics) and corrected according to the serum albumin. Allegro IRMA (Roche Diagnostics) was used to measure plasma iPTH (normal range, 15–60 pg/mL). Blood samples for iPTH were taken into cooled plastic EDTA tube kept on ice, and plasma was separated within 24 h of venepuncture. The detection limit was 1 pg/mL, and the intra- and interassay coefficient of variations was 2 and 10%, respectively. 25-hydroxyvitamin D was measured using liquid chromatography coupled with tandem mass spectrometry (Schimadzu-API LC–MS-MS API 3200, Canada) and the normal range was 20–80 µg/L). The lower and upper detection limits were 4 and 150 µg/L, respectively. Reference ranges for albumin, P, ALP, Cr, 24-h uCa, and 24-h uP excretion were 3.5–5.2 g/dL, 2.5–4.5 mg/dL, 36–113 IU/L, 0.5–1.1 mg/dL, 25–300 mg/day, and 0.4–1.3 g/day, respectively.

Posteroanterior lumbar spine and femur bone mineral density (BMD) were evaluated with DEXA (QDR-4500, Hologic Inc, Waltham, MA). BMD was expressed as *T*-score or *Z*-score. In postmenopausal women and men older than 50 years of age, *T*-scores were taken into consideration. In premenopausal women and young men, *Z*-scores were evaluated. The results were classified as normal, osteopenia, and osteoporosis according to the criteria defined by WHO. The renal US was performed to evaluate nephrolithiasis.

Conventional Ultrasonography

An Esaote Colour Doppler system (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) with a superficial probe (Model LA523 13e4, 5.5e12.5 MHz) was used for the parathyroid US. The procedure was performed in the supine position with the patient's head hyperextended and neck skin coated with acoustic material. Probes with a lower frequency were used for lesions in deeper locations. Examination was performed from the hyoid bone superiorly to the thoracic entrance inferiorly in the transverse axis and from the carotid artery to the midline in the longitudinal axis. The most common areas of parathyroid glands, such as the posterior parts of the thyroid capsule and the superior and inferior parts of the thyroid lobes, were scanned first. The medial side of the carotid artery and jugular vein and the periphery of the tracheoesophageal groove was examined. If no parathyroid lesion was detected in the expected areas, other common ectopic localizations were examined. The localization, anteroposterior (AP), transverse (T), and longitudinal (L) diameters of parathyroid lesion/lesions were recorded. The US features of the lesion with the biggest L diameter were included in the analysis in patients with PH.

Technetium-99 m-sestamibi Scintigraphy

Technetium-99 m-sestamibi (sestamibi) scintigraphy was performed using intravenous 15 mCi Technetium-99 m-methoxy-isobutylisonitrile. Anterior static images of the neck and mediastinum were obtained 10 min and 3 h after the injection. At the 3-h time point, computed tomography (CT) and/or single photon emission CT images were obtained to confirm the anatomic correlation and attenuation within the neck region. A distinct focus of increased or separate sestamibi uptakes relative to the thyroid gland on either early or late images (or both) indicated a positive result.

Conventional imaging methods such as CT or magnetic resonance imaging of the neck were used in case US and sestamibi failed to localize the lesion or these two modalities were discordant. In such cases, US-guided fine needle aspiration PTH washout was another option to establish the nature of the lesion and discriminate the parathyroid gland from thyroid lesions or cervical lymph node.

Histopathological Examination

Histopathological examination was made by an experienced endocrine pathologist. Well-circumscribed benign neoplasms of chief cells with absent or scant interspersed adipocytes were diagnosed as PA. PH was defined when there was a hyperplasia that involves more than one gland. There was a proliferation of chief cells, oncolytic cells, transitional cells, or clear cells. Intercellular adipocytes were lost between multiple lobulated nests of parathyroid cells [13, 14]. Histopathological presence of lymphovascular invasion or invasion of soft tissue, muscle, or any surrounding structures (thyroid, trachea, esophagus, and jugular vein), or documented regional or distant metastasis led to the diagnosis of PC. When absolute criteria for PC were not met, but there were two or more worrisome histological features including mitotic figures, broad intratumoral fibrous bands, necrosis, trabecular growth, and diffuse cellular atypia/pleomorphism or adherence to adjacent structures, APA was diagnosed [15]. The cases were divided into three groups as PA, PH, and PC + APA based on a combination of histopathological and clinical criteria. The study was approved by the local ethics committee of the University Hospital (11.12.2019/127). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Statistical Analysis

Three-way ROC analysis and the other statistical analyses were performed by "DiagTest3Grp" package in R programming language [16, 17] and IBM SPSS Statistics Version 21.0 for Windows (IBM Corp. Released 2012. Armonk, NY), respectively. The distributions of continuous variables were examined by Shapiro–Wilk's test and normality graphs. Because all continuous variables were not normally distributed, median (minimum–maximum) values were given. Categorical variables were presented as frequency and percent (%). Kruskal Wallis analysis and Pearson chi-square tests were used to compare quantitative and categorical variables, respectively. A p value less than 0.05 was considered as statistically significant. In case of significant difference, results were presented after (Dunn's) Bonferroni correction was applied. The Rank analysis covariance (Ranked ANCOVA) method proposed by Quade was used to control the influence of the covariates (age and gender) for all group comparisons, and the Kruskal–Wallis test was performed to compare the residuals, obtained from the linear regression of the ranked response and the ranked covariate, in groups. Three-way ROC analysis was performed to assess the performance of laboratory and US parameters to predict the histopathological diagnosis. A volume under surface (VUS) value higher than 0.17 was suggested to give information beyond chance [18]. Cut-off values and correct classification probabilities (CCP) of the three groups were calculated when the VUS value was higher than 0.17. The calculated CCP1, CCP2, and CCP3 values were probabilities to predict PH, PA, and PC + APA, respectively. The ordinal logistic regression analysis was applied to determine the combined effect of Ca, and AP and L diameter variables.

Results

There were 343 patients with PA, 20 patients with PH (4 glands involved in 10 patients, 3 glands in 4 patients, and 2 glands in 6 patients) and 35 patients with PC + APA (30 patients with AP and 5 patients with PC). There were 13 (65.0%) women in PH, 305 (88.9%) in PA, and 28 (80.0%) in PC + APA groups ($p = 0.004$). The median ages were similar in the three groups ($p = 0.074$) (Table 1). Median serum Ca, P, ALP, and PTH were significantly different between groups ($p = 0.014$, $p = 0.002$, $p = 0.011$, and $p < 0.001$, respectively). Serum 25-hydroxyvitamin D, and 24-h uCa ve 24-h uP were similar in three groups ($p = 0.610$, $p = 0.604$, and $p = 0.257$, respectively). Ultrasonographically, all three diameters were different between groups (Table 1). Binary comparisons of variables with at least one significant difference are given in Table 2.

There were 279 (70.1%) asymptomatic and 119 (29.9%) symptomatic patients. Groups were similar in terms of rate of symptomatic patients ($p = 0.107$) (Table 1). Among patients with PC + APA, 21 (60%) were asymptomatic and 14 (40%) were symptomatic. However, among 5 patients with PC, 4 (80%) were symptomatic. Median PTH

Table 1 Comparison of demographical and biochemical features of patients with parathyroid hyperplasia, parathyroid adenoma, and parathyroid carcinoma or atypical parathyroid adenoma

Variables	Parathyroid hyperplasia ($n=20$)	Parathyroid adenoma ($n=343$)	Parathyroid carcinoma + atypical parathyroid adenoma ($n=35$)	*p*	*adj. p*
Gender (woman)	13 (65.0)[a]	305 (88.9)[b]	28 (80.0)[a, b]	**0.004**	
Age (year)	47.0 (26.0; 71.0)	53.00 (20.0; 79.0)	50.0 (34.0; 82.0)	0.074	
Symptomatic	9 (45.0)	96 (28.0)	14 (40.0)	0.107	
Calcium (mg/ dL)	10.8 (9.0; 15.5)	11.2 (9.2; 18.5)	11.4 (9.4; 16.5)	**0.014**	**0.007**
Albumin (g/dL)	4.3 (3.2; 4.9)	4.5 (3.40; 5.78)	4.4 (3.5; 4.9)	0.219	0.201
Phosphorus (mg/dL)	2.9 (1.8; 9.0)	2.5 (1.1; 7.0)	2.3 (1.38; 3.9)	**0.002**	**0.003**
Creatinin (mg/dL)	0.7 (0.5; 9.47)	0.7 (0.3; 8.4)	0.7 (0.4; 4.2)	0.623	0.958
Alkaline phosphatase (IU/L)	104.0 (61.0; 776.0)	94.0 (32.0; 1163.0)	122.5 (27.0; 1880.0)	**0.011**	**0.035**
Parathyroid hormone (pg/mL)	210.5 (71.9; 2500.0)	155.5 (44.0; 3594.0)	300.0 (87.0; 1703.0)	**< 0.001**	**< 0.001**
25-hydroxyvitamin D (µg/L)	17.7 (7.6; 55.0)	16.0 (7.1; 101.0)	11.9 (7.90; 59.0)	0.590	0.610
24-h urinary calcium (mg/day)	433.0 (152.0; 947.0)	369.0 (93.8; 1438.0)	408.0 (113.00; 1191.0)	0.554	0.604
24-h urinary phosphorus (mg/day)	855.0 (490.0; 1320.0)	745.0 (0.8; 2060.0)	688.5 (33.0; 1810.0)	0.272	0.257
Ultrasonographical diameters					
Anteroposterior (mm)	8.40 (4.50; 20.30)	8.20 (3.60; 26.50)	10.45 (5.50; 30.00)	**0.001**	**0.001**
Transverse (mm)	9.50 (6.30; 17.40)	8.80 (3.90; 27.60)	12.05 (4.60; 45.00)	**0.001**	**0.002**
Longitudinal (mm)	13.90 (7.50; 23.90)	14.00 (6.90; 48.50)	18.10 (8.30; 49.70)	**0.002**	**0.003**

p value less than 0.05 are considered statistically significant

Data were presented as frequency (percentage) for categorical variables and median (minimum; maximum) for quantitative variables. *p* value was obtained from Kruskal Wallis test and adj. p value was obtained from rank analysis of covariance (adjusted for age and gender)

[a,b]Each subscript letter denotes a subset of group categories whose column proportions do not differ significantly from each other at the level 0.05 level

Table 2 Binary comparisons of variables with at least one significant difference

	PA vs PH		PH vs PC + APA		PA vs PC + APA	
	p	*adj. p*	*p*	*adj. p*	*p*	*adj. p*
Calcium (mg/ dL)	0.052	**0.026**	**0.010**	**0.005**	0.366	0.371
Phosphorus (mg/ dL)	0.122	0.090	**0.002**	**0.003**	**0.020**	**0.044**
Alkaline phosphatase (IU/L)	> 0.999	> 0.999	0.603	0.764	**0.008**	**0.029**
Parathyroid hormone (pg/mL)	**0.011**	0.063	> 0.999	> 0.999	**< 0.001**	**0.001**
Anteroposterior diameter (mm)	> 0.999	> 0.999	**0.030**	**0.020**	**< 0.001**	**0.001**
Transverse diameter (mm)	> 0.999	> 0.999	0.332	0.210	**0.001**	**0.001**
Longitudinal diameter (mm)	> 0.999	> 0.999	0.083	0.122	**0.001**	**0.002**

p value less than 0.05 are considered statistically significant

p value was adjusted pairwise comparison result from Kruskal Wallis test, *adj.p* value was adjusted pairwise comparison result from rank analysis of covariance (adjusted for age and gender)

PA parathyroid adenoma, *PH* parathyroid hyperplasia, *PC* parathyroid carcinoma, *APA* atypical parathyroid adenoma

was 198 pg/mL (44–3594 pg/mL) in symptomatic and 159 pg/mL (48.2–2800 pg/mL) in asymptomatic patients ($p=0.001$). In addition, symptomatic patients had higher median serum Ca compared to asymptomatic patients [11.46 (9.0–18.5) mg/dL vs 11.17 (9.23–15.50) mg/dL, $p=0.002$]. There was no difference in median AP, T ve L diameters of lesions between symptomatic and asymptomatic patients ($p>0.05$ for each).

There was no significant difference in rates of osteoporosis/osteopenia and nephrolithiasis between groups ($p=0.901$ and $p=0.309$, respectively) (Table 3). Parathyroid lesions were localized preoperatively in all patients with PH and PC + APA and 322 (93.9%) patients with PA ($p=0.169$). Rates of detection of lesions with sestamibi were similar in the three groups (55% in PH, 70.2% in PA, and 81.8% in PC + APA) ($p=0.114$).

Table 3 Bone mineral density, renal and parathyroid ultrasonography, and Technetium-99 m-sestamibi scintigraphy results in patients with parathyroid hyperplasia, parathyroid adenoma and parathyroid carcinoma or atypical parathyroid adenoma

Variables	Parathyroid hyperplasia *n* (%)	Parathyroid adenoma *n* (%)	Parathyroid carcinoma + atypical parathyroid adenoma *n* (%)	Pearson X^2	*p*
Bone mineral density					
Normal	4 (20.0)	74 (23.1)	9 (30.0)	1.055	0.901
Osteopenia	7 (35.0)	106 (33.1)	8 (26.7)		
Osteoporosis	9 (45.0)	140 (43.8)	13 (43.3)		
Nephrolithiasis					
Absent	10 (58.8)	248 (75.2)	23 (76.7)	2.349	0.309
Present	7 (41.2)	82 (24.8)	7 (23.3)		
Parathyroid lesion in ultrasonography					
Absent	0 (0.0)	21 (6.1)	0 (0.0)	3.555	0.169
Present	20 (100.0)	322 (93.9)	35 (100.0)		
Parathyroid lesion in sestamibi					
Absent	9 (45.0)	97 (29.8)	6 (18.2)	4.348	0.114
Present	11 (55.0)	228 (70.2)	27 (81.8)		

Sestamibi: Technetium-99 m-sestamibi scintigraphy

Three-way ROC analysis was performed to evaluate the performance of biochemical variables and US diameters to differentiate the three groups. VUS values of variables are given in Table 4. The performances of variables other than serum Ca and AP and L diameters in US were not sufficient to predict groups ($p > 0.05$). VUS values of serum Ca and AP and L diameters of lesions were significantly higher than 0.17 ($p = 0.003$, $p = 0.011$, and $p = 0.027$, respectively).

Cut-off values of serum Ca were determined as 10.73 mg/dL and 11.45 mg/dL for C_1 and C_2, respectively. C_1 was 6.00 mm and C_2 was 12.90 mm for AP diameter. For L diameter, C_1 was 14.00 mm and C_2 was 22.20 mm (Table 4) (Fig. 1). Accordingly, serum Ca < 10.73 mg/dL was predictive for PH, 10.73–11.45 mg/dL was predictive for PA and > 11.45 mg/dL was predictive for PC + APA. CCP1, CCP2, and CCP3 for serum Ca were 50.00%, 42.40%, and 48.57%, respectively. Cut-off values for AP and L diameters and CCP1, CCP2, and CCP3 values for these parameters are given in Table 4.

The ordinal logistic regression model was constructed to evaluate the combined effect for categories. There was no statistically significant effect with respect to Ca and L diameter, but the AP diameter had a statistically significant effect. When the three variables were used for classification, only two categories (PA and PC + APA) were determined. The model obtained from these three variables was not found as statistically significant (Goodness-of-fit p-value:0.038, Nagelkerke R^2: 0.088).

Table 4 Volume under surface for variables

	VUS	%95 CI (lower–upper limit)	*p*	Cut-off values C_1–C_2	CCP 1	CCP 2	CCP 3
Calcium	0.33	0.21–0.44	**0.003**	10.73–11.45	0.5000	0.4240	0.4857
Albumin	0.22	0.13–0.30	0.120	-	-	-	-
Phosphorus	0.09	0.04–0.14	0.999	-	-	-	-
Creatinin	0.22	0.10–0.34	0.191	-	-	-	-
Alkaline phosphatase	0.26	0.11–0.41	0.119	-	-	-	-
Parathyroid hormone	0.17	0.09–0.25	0.469	-	-	-	-
25-hydroxyvitamin D	0.13	0.06–0.21	0.815	-	-	-	-
24-h urinary calcium	0.16	0.06–0.25	0.568	-	-	-	-
24-h urinary phosphorus	0.09	0.03–0.15	0.996	-	-	-	-
Anteroposterior diameter	0.31	0.19–0.42	**0.011**	6.00–12.90	0.3889	0.6290	0.4688
Transverse diameter	0.23	0.15–0.32	0.058	-	-	-	-
Longitudinal diameter	0.26	0.16–0.35	**0.027**	14.00–22.20	0.5556	0.3161	0.4857

p value less than 0.05 are considered statistically significant

VUS volume under surface, *C_1–C_2* first and second cut-off values, *CCP* correction classification probabilities

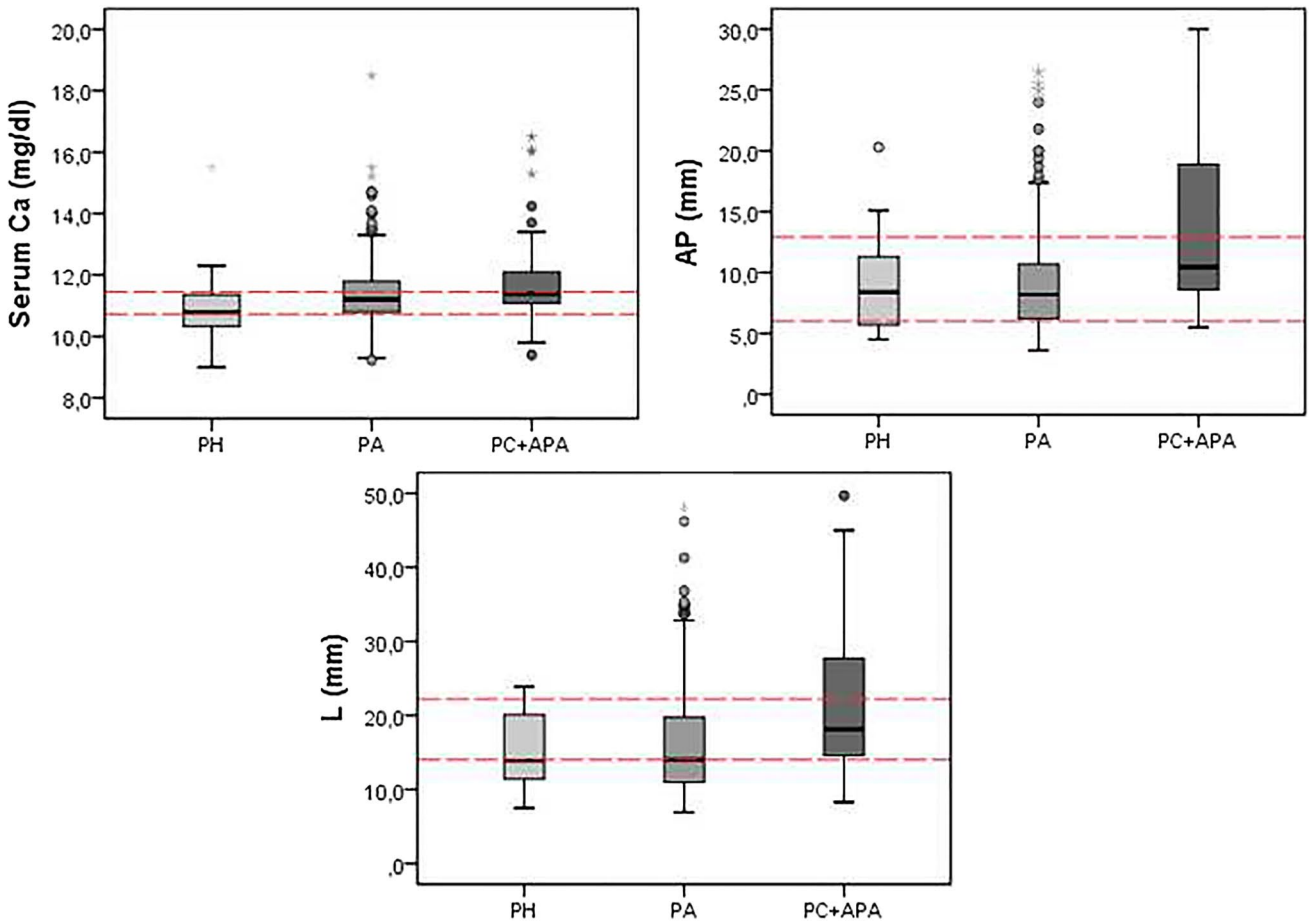

Fig. 1 Cut-off values for serum calcium, and anteroposterior and longitudinal diameters of lesions in ultrasonography (*PH* parathyroid hyperplasia, *PA* parathyroid adenoma, *PC* parathyroid carcinoma, *APA* atypical parathyroid adenoma, *Ca* calcium, *AP* anteroposterior, *L* longitudinal

Discussion

It is not possible to exactly differentiate PH, PA, APA, or PC with a single biochemical parameter or imaging feature in the preoperative period. Even, histopathological features of these lesions might overlap which makes the classification difficult and leaves the prognosis unidentified. The surgical approach for PH is more complex than PA and is associated with a higher rate of failure [19]. Although, APA is suggested to present with more severe clinical and biochemical features compared to PA, the majority of patients (96%) are cured with parathyroidectomy [20]. PC comprises a very small proportion of PHPT cases; however, it requires aggressive treatment and has a higher risk of surgical complications. Therefore, it might be helpful to differentate PC from other benign causes of PHPT preoperatively. In this study, we aimed to evaluate whether any biochemical or ultrasonographical parameter can be used to determine the histopathological diagnosis preoperatively. We showed that serum Ca and AP and L diameters of the parathyroid lesion in US were predictive for the histopathological result. In our study group, serum Ca > 11.45 mg/dL, AP diameter > 12.90 mm, and L diameter > 22.20 mm were predictive for PC + APA. Serum Ca < 10.73 mg/dL, AP diameter < 6.00 mm, and L diameter < 14 mm were predictive for PH, while values between these were predictive for PA.

In the present study, the ages of patients were similar in three groups. Although younger age was reported in PC patients compared to patients with benign parathyroid lesions in some previous studies, there are also some others that observed no difference in age [21, 22]. In a study from our clinic, the age of patients with PA, APA, and PC was similar, while the rate of women was higher in PA, and rates of men were higher in APA and PC [23]. In contrary, in another study, women were predominant in both PA and APA patients, and men were predominant in PC patients [24]. In a study including 464 PA and 38 PH patients, the age and sex distribution were similar in the two groups [25]. Woman predominance in the PA and PH groups and man predominance in the PC group were reported in a study; however, there was no statistically significant difference in gender distribution in each of the three different groups

[26]. In our study, women predominated men in all three groups. The rate of women was significantly higher in the PA group compared to the PH group, while it was similar in the PC + APA group with both PA and PH.

It is difficult to discriminate PA, PH, APA, and PC biochemically. Although hypercalcemia is generally mild in PHPT (serum Ca < 11 mg/dL), values higher than 13 mg/dL may also be seen more commonly in patients with PC [27]. The biochemical profile of patients with APA is suggested to be more similar to that of patients with PC than PA [20]. There are studies comparing biochemical findings in different histopathological groups in the literature. To our knowledge, this is the first study to include 4 histopathological groups of PHPT (PH, PA, APA, and PC). In a study, serum Ca levels were significantly higher in the PC group compared with the APA and PA groups, and serum PTH levels were higher in the PC and APA groups compared with the PA group. However, serum P levels were similar in the three groups. The authors reported that the cut-off values of Ca, PTH, ALP, and UCa that can discriminate APA and PC were 12.45 mg/dL, 265.05 pg/mL, 154.5 IU/L, and 348.5 mg/ day, respectively [23]. Serum Ca, iPTH, creatinine, P, and ALP were significantly higher in PC than the PA and PH groups, and serum ALP level higher than 285 IU/L was predictive for the diagnosis of PC in a Korean study [26]. In another study, mean Ca was significantly lower in PH than PA (11.2 SD1.1 mg/dL vs 11.5 SD 0.9 mg/dL), while mean PTH was similar [25]. In the present study, median Ca was higher in PC + APA compared to the other two groups; however, the difference was statistically significant only between PC + APA and PH. PC + APA group had significantly higher PTH than PA, and the PA group had significantly higher PTH than PH. For ALP, the difference was significant between PC + APA and PA. Serum P was lower in PC + APA group compared to both PA an the PH groups. Despite differences in serum Ca, P, ALP, and PTH between groups, serum Ca was the only significant variable that can be used to predict histopathological diagnosis. Serum Ca < 10.73 mg/dL, 10.73–11.45 mg/dL and > 11.45 mg/dL were predictive for PH, PA, and PC + APA, respectively.

The clinical features of PHPT are nephrolithiasis, fatigue, bone pain, brown tumor, and depression. Not any of these signs are specific for patients with PA, PH, APA, or PC. The effects of PC on bone and kidneys are generally more severe than other benign causes of PHPT, probably due to the higher degree of hypercalcemia [28–31]. It is known that most patients with PHPT are asymptomatic and diagnosed incidentally during a routine laboratory examination. Still, some patients with benign causes of PHPT can present with more severe manifestations [32–34]. Thus, overlapping clinical features in patients with PC and patients with benign causes of PHPT make it nearly impossible to differentiate malignancy from benign diseases using the clinical manifestations. In a previous study, patients with PC and PA/PH had similar clinical symptoms, bone loss or fracture and nephrolithiasis [26]. Similarly, no difference was reported in the rates of osteoporosis and nephrolithiasis between patients with PH and single PA [25]. In accordance with previous studies, the rates of osteoporosis and nephrolithiasis were also similar in PC + APA, PA, and PH groups in our study. Although, the frequency of symptomatic patients in the PA group was lower than PH and PC + APA, the difference was not statistically significant.

Concordant use of US and scintigraphy can detect solitary adenomas with a sensitivity of approximately 100% [35]. It was shown that sestamibi scintigraphy was positive in 65.6% of PA, 78.3% of APA, and 100.0% of PC patients [23]. In another study comparing PA and PH, PH was associated with both false negative sestamibi scintigraphy and US. True positive sestamibi scintigraphy was observed in only 3% of PH patients while it was positive in 79%, and US was positive in 78% of single PA cases. The authors concluded that a negative result on both sestamibi scintigraphy and US was strongly correlated with PH [25]. In our study group, we localized parathyroid lesion in 100% of PH, 93.2% of PA, and 100% of PC + APA with US. For sestamibi scintigraphy, the rates of positivity were 55.0% for PH, 70.0% for PA, and 81.8% for PC + APA lesions, and there was not any significant difference between groups. A high detection rate of PH with US might be suggestive for high false positivity of US. However, we did not calculate the false positivity or negativity of imaging methods in our study. This may constitute one of our study limitations.

The size of a parathyroid tumor may help to predict histopathological diagnosis in a patient with PHPT. In a recent review, the median size of APA was reported as 2.5 cm (range 0.7–7.2 cm) [20]. The cut-off value of diameter for PC was determined as 3 cm and 3.3 cm in two previous studies [28, 36]. In another study, tumor size was higher in patients with PC compared to patients with benign parathyroid diseases (3.8 SD1.6 cm vs 1.7 SD0.8 cm) [26]. In our study, we observed that the median L diameter of PA and PH groups were similar, while it was higher in the PC + APA group than PA group. In addition, both AP and L diameters were correlated with histopathological diagnosis. AP diameter > 12.90 mm and L diamater > 22.20 were predictive for PC + APA, while AP diameter < 6.00 mm and L diameter < 14.00 mm were predictive for PH. The values in between predicted PA.

The Ca, AP diameter, and L diameter variables had significant classification rates for categories. When the combined effect from these three variables was evaluated, only the AP diameter was found as statistically significant. The classification rate of AP diameter for PA was 62.9%; the classification rate for PH was 38.89%, and the classification rate for PC + APA was 46.88%.

There are a number of limitations in our study. Firstly, it is a case series analysis performed in a single center. Secondly, US was performed by three different endocrinologists. Moreover, the number of patients with PC was small. Ionized Ca is a more valuable parameter to evaluate serum Ca concentration. Unfortunately, we did not have the opportunity to measure ionized Ca in our study group. However, since it is not available in most centers and its measurement is costly and technically challenging, corrected total serum Ca is suggested to be an appropriate first-line biochemical test for the diagnosis of PHPT by many experts [11]. The combined classification probabilities for clinical variables should be examined in studies where the sample size would be sufficient for subgroups. Lastly, the lack of follow-up data about persistent or recurrent hypercalcemia particularly in patients with PH can be considered as another limitation.

Conclusions

In conclusion, the diagnosis of PH is often challenging and preoperative localization studies may not always help to detect the hyperplastic parathyroid glands. APA is a group of intermediate form of parathyroid neoplasms with uncertain malignant potential which show some atypical histological features. Both PC and APA lesions may appear firm and adherent to the adjacent structures intraoperatively directing the surgeon to more aggressive surgery. Predicting the histopathological diagnosis in the preoperative period is very valuable for the clinician in terms of determining the surgical approach and clinical follow-up. In this study, we showed that, although not very decisive, in the presence of preoperatively high serum Ca and big lesions in US, the possibility of PC and APA should be considered, while mildly increased Ca and smaller lesions might be suggestive for PH.

Data Availability The data that support the findings of this study are available from the corresponding author (D.O) upon reasonable request.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Ankara Yildirim Beyazit University (Approval date and number: 11.12.2019/127**).**

Conflict of Interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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