Annals of Diagnostic Pathology 46 (2020) 151492

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Radiological-Pathological Correlation

Mapping of parathyroid neoplasms based on grey scale ultrasound images and histopathological whole slide images

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ARTICLE INFO

Keywords:
Parathyroid
parathyroid adenoma
ultrasound
echogenicity
cystic
whole slide imaging

ABSTRACT

Purpose: In this study, echogenicity and histopathological projections of parathyroid neoplasia in grey mode ultrasonography were compared with whole side imaging (WSI). The utility of the data obtained for clinical assessment was evaluated.

Methods: In 57 patients operated for hyperparathyroidism, the parathyroid gland was sampled in the sagittal plane. The lesion slides were scanned. The WSI was rendered digital. The histopathological slide images scanned with USG images were matched. With the İmage J program, the areas of cell types and morphological changes were measured.

Results: In parathyroid neoplasms, hypoechoic areas were found to be matched with 21% [55.3%] chief cell, 2 [5.0%] oncocytic cell and 8%[20.0%] cystic morphology. Of the 57 patients, 26 [45.61%] had a cystic area. It was seen that hyperechogenic areas match more connective tissue areas than chef cell [$p < 0.05$]. There was less clear cell in hyperechogenic areas than iso-hyperechogenic areas [$p < 0.05$]. The ratio of fat tissue echogenicity was lower in hypoechoic areas than hyperechoic [$p < 0.05$]. There was a positive correlation between PTH and the entire tissue area [$r = 0.377$, $p = 0.004$]. A positive directional moderate linear relationship was found between blood calcium level and parathyroid adenoma [rho = 0.530, $p = 0.009$] and percentage [rho = 0.416, $p = 0.048$]. When atypical adenomas and adenoma cases were compared, no significant difference was found between the cystic and chief cell areas [$p > 0.05$].

Conclusion: The hypoechogenicity seen in USG was observed to be compatible with chief cell, hyperechogenic areas in USG were compatible with connective tissue and fat tissue. As the cystic area increased, blood calcium levels were higher in adenomas. We think that the results of this study will be guiding to evaluate the reflections of the detailed morphometric studies.

1. Introduction

Parathyroid neoplasms are classified as parathyroid adenomas, parathyroid carcinomas, secondary tumours, mesenchymal tumours and very rare tumours according to WHO [1]. Eighty-five percent of primary hyperparathyroidism worldwide is caused by parathyroid adenomas with a single gland [1]. Ultrasonography [USG] has an important role in the clinical diagnosis of parathyroid lesions. Parathyroid adenomas are well-circumscribed solid lesions with a subtle echogenic rim showing oval or lobulated, hypoechoic, homogeneous echotexture. Isoechogenicity or hyperechogenicity, heterogeneous structure, cystic change, and calcification are atypical images of parathyroid ultrasound [2]. Parathyroid tissue generally consists of chief cells. It may contain oncocytic cell, transitional cells and clear cells. Parathyroid glands contains %10–30 adipocytes [3]. This study was planned to see how the reflection of the cell types and morphological changes in the lesions, which form parathyroid lesions, on ultrasound images will help in the clinical assessment.

In order to compare the histopathological projections of the parathyroid neoplasms with the grey mod USG echogenicity, the whole surface imaging [whole slide image, WSI] method of the parathyroid neoplasms was used. Areas consisting of different cell types in parathyroid neoplasms were marked using the Image J computer program on WSI images. In the same way, the morphological changes such as

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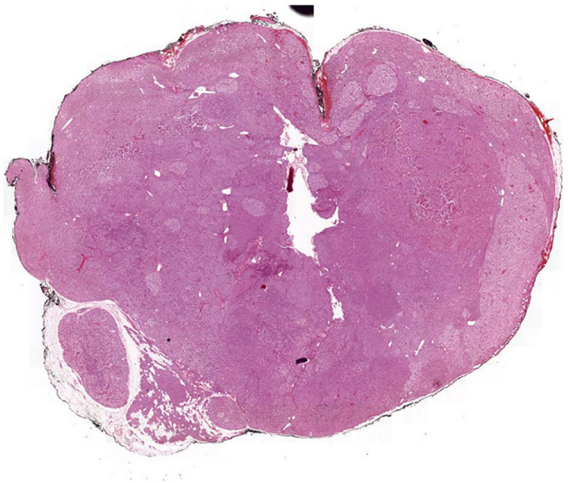
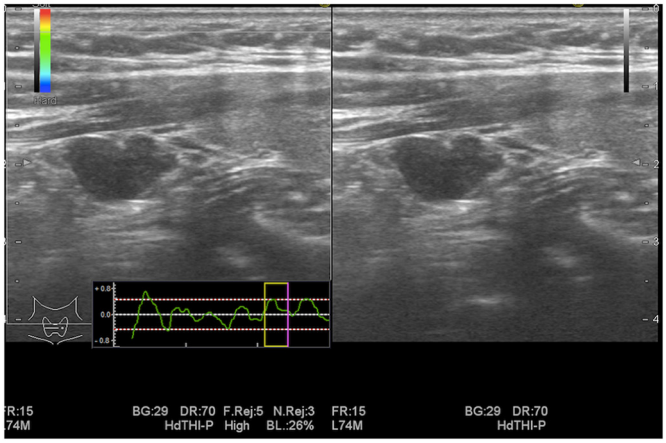
https://doi.org/10.1016/j.anndiagpath.2020.151492

haemorrhage, cystic changes were marked using the area measurement feature of Image J computer program. Cell types and morphological features of parathyroid neoplasms were correlated with ultrasonography and laboratory findings.

2. Methods

Parathyroid specimens were sampled in the sagittal plane macroscopically in 57 patients operated for hyperparathyroidism. Histopathological examination was performed in light microscopy. Patients who did not clearly show invasive features according to WHO criteria but showed some features of parathyroid carcinoma were defined as atypical parathyroid adenoma [1]. Parathyroid tissues are neuroendocrine tissues [2]. Therefore, the cases were evaluated by light microscopy with parathormone [PTH] and the most specific neuroendocrine marker chromogranin A immunohistochemically staining. The lesion slides were screened using a special interface software and a JPEG2000 image compression and coding system in the Zeiss AX10 motorized light microscope. All surface parathyroid lesions were rendered digital image. The system was created in a client-server architecture that stores high-resolution slideshows and enables real-time viewing, compressing without compromising picture quality. The system consisted of a motorized microscope, a motorized table, a robotic slide loader, and a high resolution camera. The slide placed on the motorized plate is automatically scanned at the desired lens and creates a high resolution image. This image was opened and viewed with the help of an interface. In WSI images, areas consisting of chef cells and oncocytic cells were mapped on the image with the help of the drawing component of Image J computer program [Fig. 1]. The same marking was performed within the cystic areas and haemorrhagic areas. A 10 mm long line marked on slides was used as a reference measure. Using this reference measure, the area measurement of the Image J computer program and the area of the cell types marked on the WSI and the other morphological changes were measured. The slide image scanned with USG images was matched with the manufacturer's [Argenite] software. For pairing, the experienced endocrinologist and





Figs. 2 and 3. WSI and USG image of paired parathyroid adenoma.

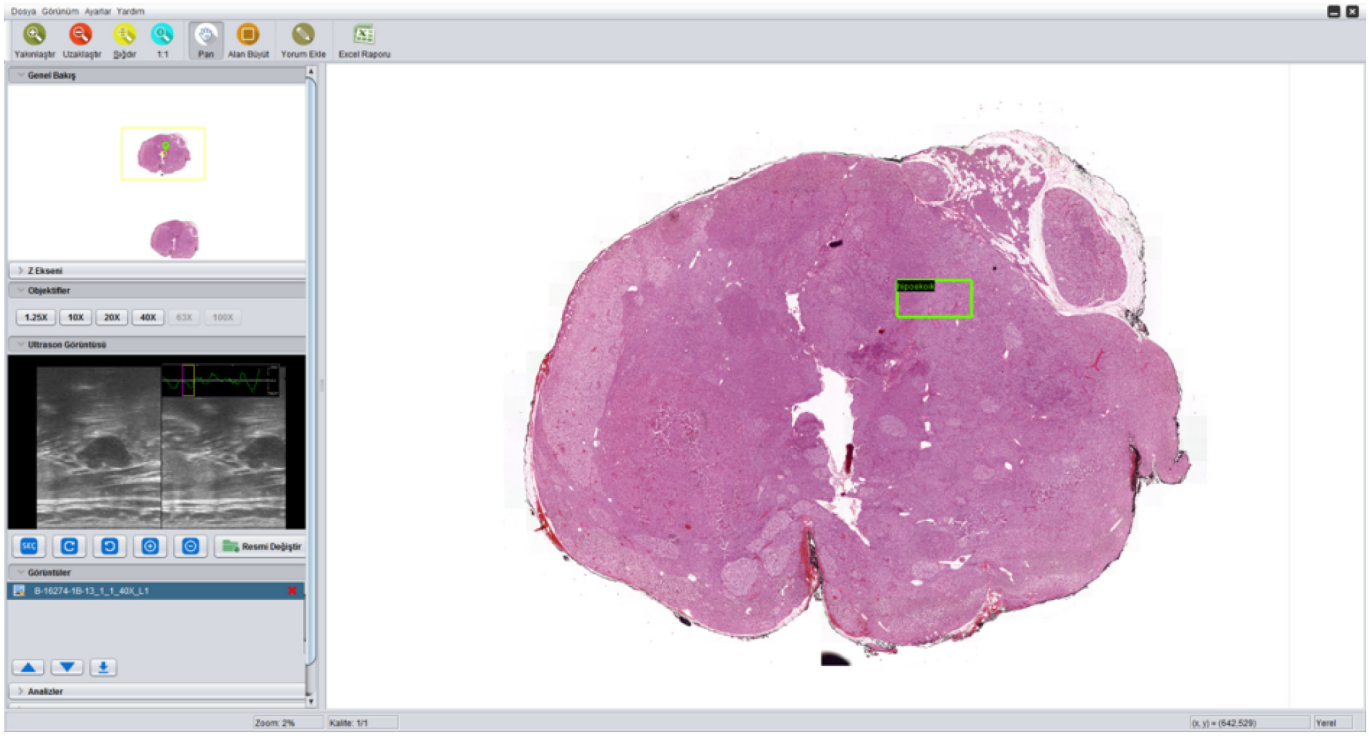


Fig. 1. In WSI images, areas consisting of chef cells and oncocytic cells were mapped on the image with the help of the drawing component of Image J.

pathologist evaluated the parathyroid USG together [Figs. 2 and 3]. In the parathyroid lesions, the corresponding areas of the different echogenic areas of USG in histopathological scanned projections of the cases were marked with the help of the Image J computer program. Cell types and morphological features of the parathyroid lesions were recorded with echogenicity characteristics.

Age, sex, preoperative PTH and calcium levels of the cases were used to compare the data.

2.1. Statistical analysis

The distributions of the continuous variables were examined by Shapiro-Wilk's test and normality plots. Median (min-max) was reported for all metric variables. Echogenicity and cell-tissue features were summarized by frequency (%).

The cell-tissue features were compared regarding echogenicity by chi-square test. Monte-Carlo simulation based on 10,000 samples was also performed since there were too many frequencies < 5. Cystic cell and chief cell areas were compared between atypical and normal tissues by Mann-Whitney *U* test. Spearman correlation analysis was used to reveal the relationship between age, PTH and calcium levels, and tissue areas. The association of the percentages of chef cell and oxyphilic cell fields with PTH was evaluated by multiple correlation coefficient. A p-value < 0.05 was considered as statistically significant.

All statistical analysis and calculations were performed via IBM SPSS Statistics 21.0 [IBM Corp. Released in 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.].

3. Results

Out of 57 patients, forty-two women were aged between 21 and 83 years, with a mean age of 53. The median PTH of the patients was 194 [min-max: 53–2800] and the median of the whole tissue area was calculated as 96.29 [min-max: 16.01–576.05] [Table 1].

In grey-scale USG imaging, echogenicity was grouped as hypoechoic, isoechoic, hyperechoic, isohypoechoic and isohyperechoic. Among the parathyroid adenomas, 21 [55.3%] chief, 2 (% 5.0.0) oncocytic cells and 8 [20.0%] cystic tissue matched the hypoechoic echogenicity [Table 2]. Adenomas with echogenicity were hyperechogenic, and chief cells were found to have lower rates of connective tissue than others ($p < 0.05$). Adenomas which are hyperechogenic were found to have a less clear cell area than isohyperechogenic [$p < 0.05$]. The rate of fat tissue was lower in hypoechoic adenomas than in hyperechoic ones in USG [$p < 0.05$]. There was no significant difference between oncocytic cells and echogenicity groups for bleeding. The connective and fat tissue areas were significantly more hyperechogenic in USG [$p < 0.001$].

No significant difference was found between echogenicity groups in terms of oncocytic cells and bleeding areas.

Age was negatively correlated with the percentage of chef cell tissue area, weakly linear [rho = −0.315, p = 0.019], but not linearly correlated with other tissue areas [$p > 0.05$] [Table 3]. The level of PTH was negatively correlated with the percentage of chef tissue area, weak, linearly related [rho = −0.353, p = 0.010], which was positively correlated weakly with the whole tissue area as linearly weak [rho = 0.377, p = 0.004]. The multiple correlation coefficient calculated for the relationship between the percentages of chef cell and oxyphilic cell fields together with PTH was found as 0.328, p = 0.476. According to this, there was no statistically significant relationship between these two cell area percentages and PTH level.

Cystic space was present in 27/57 [47,36%] of our parathyroid adenoma cases. There was a moderate positive correlation between blood calcium level and parathyroid adenoma [rho = 0.530, p = 0.009] and percentage [rho = 0.416, p = 0.048]. No relationship was found.

There was no significant difference between, atypical parathyroid adenoma and adenoma cases in terms of cystic and chief cell areas [$p > 0.05$] [Table 4].

4. Discussion

The histopathological comparison of hypoechoic echogenicity in USG in with parathyroid neoplasms was observed to be mostly matched with chef cell areas and cystic areas. This data was not statistically significant. It was thought that the small number of cases could cause this. Parathyroid lesions in USG evaluation, parathyroid adenoma is considered to be hypoechoic, well-defined, homogenous echotexture, solid lesions [2,4]. Cell fields are also seen in other echogenic patterns, especially isoechogenicity. It is notable that only the hyperechogenic pattern matched with the least significant pattern [$p < 0.001$]. When a hyperechogenic site is observed in a parathyroid lesion, we can consider that this area does not represent chef cells. Although the hypoechoic echogenicity of parathyroid adenomas is often attributed to the homogeneous monitoring of the chef cells in publications [5,6]. In our comparison, it is noteworthy that they have a significant hypoechoic structure in cystic areas. Chandromoan and his friends. Have described the diagnostic criteria for cystic parathyroid adenoma as an anechoic lesion with posterior and acoustic expansion. They describe a solid lesion with multiple anechoic areas in the parathyroid adenomas as cystic degeneration [2].

In our cases, it was seen that connective tissue and fat tissue areas were observed to be hyperechogenic [$p < 0.001$]. However, it is seen that connective tissue areas can be observed in isoechoic and hypoechoic echogenicity. Chandromoan et al. in their study, haemorrhage, hyalinization and fibrosis were observed in 5 isoechoic lesions and 1 hyperechoic lesion in histological evaluation [2]. Haemorrhage, fibrosis and oedema cause heterogeneous echotexture. Parathyroid adenomas with greater hyperechogen area may be more likely to be atypical, and therefore, clinical follow-up can be performed more closely. These cases may be candidates for CDC73 mutation evaluation. It may be thought to investigate this in more atypical and normal parathyroid adenomas.

In our study, as the age of the cases increased in parathyroid adenomas, the chef tissue area in the lesion decreased weakly, but it was not associated with other types of tissue. The increase in age of oncocytic cells as well as the increase in degenerative changes such as cystic changes may be considered as the reason for this. However, in our study, there was no specific linear correlation between the presence of clear cells, the presence of oncocytic cells and the presence of cystic areas.

Table 1
Demographic features.

	Age	PTH	CA	Chief cell area		Onkocytic area		Cystic area		Whole area
					%		%		%	
n	57	55	52	22		18		27		57
Median	53.0	194.0	11.66	11.61	14.67	5.41	5.31	10.77	10.38	96.29
Minimum	21.0	53.0	8.80	1.46	0.61	0.40	0.37	0.79	1.88	16.01
Maximum	83.0	2800.0	18.50	155.86	100.0	129.66	93.65	190.22	77.07	576.05

Table 2
Distribution of cell types and morphological changes according to echogenicity.

	1	2	3	4	5	p
Chief cell	21 [55.3]	14 [82.4]	1 [5.9][a]	9 [69.2]	4 [57.1]	< **0.001**
Oncocytic cell	2 [5.0]	0 [0.0]	0 [0.0]	2 [15.4]	1 [14.3]	0.201
Clear cell	3 [7.5]	4 [22.2]	0 [0.0][b]	3 [23.1]	3 [42.9][b]	0.025
Connective tissue	3 [7.5]	4 [22.2]	12 [70.6][a]	0 [0.0]	0 [0.0]	< **0.001**
Cystic area	8 [20.0]	0 [0.0]	0 [0.0]	0 [0.0]	1 [14.3]	0.008
Lipocytes	0 [0.0][b]	2 [11.1]	6 [35.3][b]	0 [0.0]	0 [0.0]	< **0.001**
Bleeding area	4 [10.0]	2 [11.8]	0 [0.0]	1 [7.7]	0 [0.0]	0.552

[a] Comparison with other rates $p < 0.05$.
[b] $p < 0.05$.

Blood PTH levels are positively correlated with the entire tissue area, positively correlated with the weak linearity. This also shows us that the production of parathormone is not merely of chef cell origin. In normocalcemic cases, oxyphilic cells produce > 50% of PTH. Respond to elevated levels of blood calcium, PTH levels provide suppression and calcium flow response [7].

The most interesting result in our study was findings related to cystic formation seen in parathyroid adenomas. In 27/57 [47,36%] of our cases, there was a micro cystic area in the parathyroid neoplasms. In the study of Acar T. et al., 9/47 [16%] cases exhibited a cystic area in parathyroid adenomas. In this study, only the USG evaluation was performed and there was no one-to-one comparison with the histopathological projection of the cases [5]. In the study of Mc Coy KL. and his friends, cystic parathyroid adenoma was observed in 48/1769 [2%] patients [8]. In the series of Chandromoan et al., the incidence of cystic changes in parathyroid adenomas is 6.4% [2]. In the series of 907 patients by Hu Ya et al., the number of cases with cystic degeneration of > 50% in the parathyroid adenomas was 37/907 [4,1%] and the number of cases with micro cystic changes was 82/907 [9]. It is seen that there is a higher rate of cystic or micro cystic component in the parathyroid adenomas. In our study, it was possible to determine minor cystic changes due to the one-to-one comparison of USG images with histopathological sections. It is thought that the cause of the development of cystic parathyroid lesions may be the degeneration of long-existing and large-sized parathyroid lesions due to insufficient vascular feeding [2].

Parathyroid cysts may be functional or non-functional. Non-functional cysts tend to be unilocular. Functional cysts have a more complex cystic appearance. Functional parathyroid cysts are thought to be due to previous haemorrhage and cystic degeneration in parathyroid adenomas. Functional and non-functional cysts also show high PTH levels in cyst fluid [10]. Most of the parathyroid cysts are solitary. 80% of cases are non-functional in female patients. In parathyroid cysts with non-functional are thought to be developmental onto genic formations that develop from the 3rd and 4th branchial clefts. Non-functional cysts show lymphoid tissue, thymus tissue, adipose tissue in the walls. This is a finding that confirms this hypothesis. The other hypothesis in the formation of cysts is the combination of micro cysts and macro cysts.

Table 4
Comparison of atypical parathyroid adenomas and parathyroid adenomas.

	Atypical adenoma	Paratiroid adenoma	p
ş_percent	*n* = 3	*n* = 19	–
Median [min-max]	4.42 [4.17–33.21]	14.77 [0.61–100]	
o_percent	*n* = 2	*n* = 15	–
Median [min-max]	9.67 [1.33–18]	5.31 [0.37–93.65]	
k_percent	*n* = 7	n = 19	0.334
Median [min-max]	9.02 [1.88–35.05]	10.5 [3.83–77.07]	
C_percent	*n* = 9	*n* = 486	0.820
Median [min-max]	82 [57.77–98.12]	88.82 [6.35–100]	
ş	n = 3	n = 19	–
Median [min-max]	15.55 [7.49–37.23]	9.28 [1.46–155.86]	
O	n = 2	n = 15	–
Median [min-max]	7.69 [4.69–10.69]	4.82 [0.4–129.66]	
k	n = 9	n = 48	0.866
Median [min-max]	10.11 [0.79–79.69]	11.42 [1.3–190.22]	
b	n = 9	n = 48	0.092
Median [min-max]	135.71 [41.62–351.16]	86.83 [16.01–576.05]	

Micro cysts may arise from local degeneration of the gland or retention of colloid secretion [11]. Lima et al. reported expression of PTH-associated peptide receptor 1 in parathyroid cysts. It may be involved in the proliferation of this lesion [11].

Functional cystic parathyroid adenomas may occur with malignant hypercalcemia or hypercalcaemic crisis [9]. This may be due to the rupture of cystic areas. In the series of Hu Ya et al., hypercalcaemic crisis was higher in cystic adenoma cases than in solid adenomas [$p < 0.027$] [9]. The hypothesis of the formation of parathyroid cysts has been proposed as the formation of macro cystic structures by combining micro cysts [17]. In our study, we found a positive linear relationship between blood calcium and cystic area. In the case series of Hu et al. blood PTH and calcium levels were found to be high in cystic parathyroid adenomas. [9] Postoperative symptomatic hypocalcaemia developed in 47% of the patients with cystic lesions [2]. Chandromoan et al. indicated a significant positive correlation between serum PTH and cystic degeneration [2]. In our study, we did not find a significant relationship between PTH serum levels and cystic area measurements.

In the series of Hu et al., cystic adenomas have more atypical

Table 3
Correlation analysis results.

	Age			PTH			Calcium		
	rho	p	n	rho	p	n	rho	p	n
Clear cell area	0.087	0.699	22	−0.062	0.785	22	0.262	0.239	22
Clear cell area %	0.197	0.380	22	−0.206	0.359	22	−0.329	0.134	22
Oncoytic area	−0.049	0.848	18	0.307	0.307	17	0.038	0.885	17
Oncocytic area %	0.257	0.319	17	0.146	0.590	16	−0.113	0.676	16
Cystic area	−0.203	0.319	26	0.387	0.056	25	0.530	0.009	23
Cystic area %	−0.057	0.783	26	0.260	0.209	25	0.416	0.048	23
Chef cell area %	−0.315	0.019	55	−0.353	0.010	53	−0.185	0.197	50
Whole area	−0.118	0.382	57	0.377	**0.004**	55	0.190	0.178	52

adenoma than solid adenomas [5,4 versus 24,3%] [9]. In the Cakir B. et al.'130 patient's series, isoechoic large lesions or cystic appearance is considered to be useful for estimation of diagnosis of atypical adenoma or parathyroid carcinoma [12].

Studies about the role of calcium in polycystic kidney disease suggest that there may be a similar relationship in the development of cystic formations in parathyroid neoplasms. The polycystin 2 integral membrane protein encoded by the PKD2 gene is located in the endoplasmic reticulum. Calcium acts as a transient cation channel and the PC2 channel responds to fluid flow changes. Interruption of this complex disrupts the flow of intracellular calcium [13]. Mangolini et al. reported that calcium channel activity was impaired and intracellular calcium signal changes due to imbalance in polycstin complex which is a membrane receptor protein. This change leads to aberrant cell proliferation and apoptosis; their views on the development and growth of renal cysts are very interesting [13]. It is understood that the imbalance between pro-apoptotic and pro-proliferative factors plays a critical role in the development of cystic kidney disease [14]. It is thought that dysregulation of epithelial cell apoptosis and proliferation in cyst development and tissue remodelling is a general mechanism that is more important than apoptosis expression level [14]. A similar change may also apply to parathyroid cystic lesions. The relationship between the role of calcium in the cell in parathyroid lesions and the relationship between cystic formation is open to research.

Parathyroid adenomas that generate primary hyperparathyroidism [HPT] can be seen in several genetic syndromes (such as MEN) or in some genetic abnormalities. There is a 10% genetic predisposition in primary HPT cases [15] One of the most known genetic deviations is the mutation in the tumour suppressor gene CDC 73 [HRPT2]. HRPT2 gene is located at 1q31.2, 17 exons, 133 kb is a gene [16,17]. Hyperparathyroidism jaw tumour syndrome (HPT HRJT), a rare syndrome seen in the HRPT2 gene mutation encoding parafibromin, is observed [18]. This mutation in particular affects the parathyroid gland. In HPT JT syndrome, parathyroid adenoma or carcinomas, as well as mandibular and maxilla fibroosseus lesions, renal cysts and tumours are also observed. Hyperparathyroidism in this syndrome is observed with more severe hypercalcemia and hypercalcaemic crisis than in MEN syndrome [17]. CDC73 mutation is the most common genetic aberration seen in parathyroid carcinomas. Pathogenic germline can also be observed as a mutation. Germ line mutation analysis is recommended for patients with HPT-JT syndrome, familial primary hyperparathyroidism, all parathyroid carcinoma cases, atypical parathyroid adenomas, and young patients with sporadic hyperparathyroidism all under 35 years [15].

Parathyroid neoplasms showing a loss of parafibromin expression parathyroid neoplasms have been shown to be a different morphology. It should be noted that these appearances are not rare in general parathyroid adenomas. These changes are layer-like growth in neoplastic cells, occasional branching vascular structures, eosinophilic cytoplasm tumour cells, perinuclear cytoplasmic transparency, micro cystic changes [16]. Juhlin et al. Cystic changes were found to be seen in large adenomas and HPT-JT syndrome [3,18]. The mechanism by which the HRPT2 mutation leads to cystic formation is an open subject.

5. Conclusion

In our study, the morphological image obtained by WSI method in parathyroid neoplasms and their projections in USG were compared. The hypo echogenicity seen in USG was observed to be compatible with chief cell in histopathology, and hyper echogenic areas in USG were compatible with connective tissue and fat tissue. It was observed that the WSI method was more suitable for morphometric studies and comparative studies with imaging methods. We think that the results of this study will be guiding to evaluate the reflections of the detailed morphometric studies. It was seen that macro and micro cystic changes observed in parathyroid adenomas were found to be more than expected. As the cystic area increased, blood calcium levels were higher in adenomas. The fact that this change is related to blood calcium level correctly suggests that the mechanisms of polycystic kidney disease are similar in cystic parathyroid adenomas.

Funding

Funded by Yıldırım Beyazit University as scientific research project, Grant No: 2805.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Research Ethics Committee of the Yıldırım Beyazit University Ataturk Research and Training Hospital approved the protocols. Due to the retrospective nature of the study, informed consent was waived.

Declaration of competing interest

The authors declare they have no conflict interest.

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