

Parathyroid incidentalomas detected during thyroid ultrasonography and effect of chronic thyroiditis on false positive parathyroid lesions

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Abstract We aimed to determine the prevalence of parathyroid incidentalomas in patients referred for thyroid ultrasonography (US) and investigate the role of chronic thyroiditis on false positive lesions. Patients suspected to have parathyroid lesions during thyroid US were recorded prospectively between August 2009 and January 2010. Patients referred for parathyroid US and patients with known high serum calcium or parathyroid hormone (PTH) levels were excluded. Suspected parathyroid lesions were defined as hypoechoic, homogeneous, solid lesions with regular margins located outside the thyroid lobe, most commonly inferior to the thyroid gland. Thyroid US was performed in 6,528 patients. There were 78 patients (1.19 %) (73 female and 5 male) with suspected parathyroid lesion. The diagnosis of a true parathyroid adenoma was confirmed in 6 (7.69 %) patients. In patients with true adenoma, mean serum calcium, phosphorus, and PTH levels were 10.57 ± 0.48 mg/dl, 3.03 ± 0.52 mg/dl, and 182.91 ± 46.62 pg/ml, respectively. Among 72 patients with false positive parathyroid lesion, antithyroid peroxidase antibody was positive in 50 (69.4 %), antithyroglobulin antibody was positive in 46 (63.9 %), and one of these antibodies were positive in 59 (81.9 %) patients. Also, 46 (63.9 %) of these patients had thyroid dysfunctions (43 hypothyroidism and 3 hyperthyroidism) and 59 (81.9 %)

had chronic thyroiditis ultrasonographically. Parathyroid incidentaloma was detected in 0.09 % of patients referred for thyroid US. The presence of clinically or ultrasonographically chronic thyroiditis might cause inadvertent interpretation of a hypoechoic lesion as a parathyroid pathology during thyroid US.

Keywords Parathyroid incidentaloma · Chronic thyroiditis · Thyroid autoantibodies · Lymphadenopathy

Introduction

The rapid development and widespread use of imaging techniques has resulted in an increased frequency of clinically silent lesions in various organs. These incidentally found lesions are termed incidentalomas and they can be unexpectedly identified during a routine physical examination, imaging procedures (computed tomography, magnetic resonance imaging, or ultrasonography) or surgical exploration performed for an unrelated reason. Incidentalomas are commonly observed in endocrine organs. Adrenal, pituitary, and thyroid incidentalomas are well defined in the literature. Most of these lesions are hormonally inactive benign tumors and do not pose any problem in long term follow-up. However, they should be managed and followed according to the specific schedules developed for each of these incidentalomas because some may be related with significant hormone-secreting diseases and malignant lesions. An adrenal incidentaloma may be associated with pheochromocytoma or Cushing's disease and a pituitary incidentaloma may disclose a prolactinoma. Diagnosis of thyroid cancer in a patient with thyroid incidentaloma is not very rare. In contrary to these well-known incidentalomas in endocrinology, few clinical studies and

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case reports describe parathyroid incidentalomas. Also, different from other endocrine gland incidentalomas which are mostly discovered in imaging studies, parathyroid incidentalomas were often reported to be identified during surgical interventions [1–3]. In the literature, two studies have investigated the prevalence of parathyroid incidentalomas detected during thyroid US [4, 5]. Parathyroid pathology was confirmed histopathologically or with high parathyroid hormone (PTH) measurements in fine needle aspiration (FNAB) washouts in these studies. Accordingly, parathyroid incidentaloma was reported to occur in 0.4 and 0.53 % of patients and positive predictive value of US to detect parathyroid incidentalomas was very low (21.4 and 24 %).

In this prospective study, we aimed to investigate prevalence of incidental parathyroid pathologies detected during routine thyroid US and prevalence of clinically or ultrasonographically chronic thyroiditis in these patients.

Materials and methods

Patients suspected of having parathyroid lesions during routine thyroid US between August 2009 and January 2010 in our out-patient clinic were recruited for this prospective study. Patients with known high serum calcium (Ca) or PTH levels and patients referred for parathyroid US were excluded. All patients gave informed consent and local ethical committee approval was obtained in accordance with the guidelines in The Declaration of Helsinki.

US was performed by the same examiner using an Esaote Technos-MPX, (Geneva, Italy) LA523 with a 13–4 MHz probe. The presence and number of thyroid nodules were recorded. Ultrasonographically, chronic thyroiditis was diagnosed when thyroid size is reduced or normal and displaying an inhomogeneous hypoechoic texture. Suspected parathyroid lesions were defined as hypoechoic, homogeneous, solid lesions with regular margins located outside the thyroid lobe, most commonly inferior to the thyroid gland. In patients with suspected parathyroid lesion, age, sex, thyroid hormonal status, medications including thyroid hormones were recorded. Serum PTH, Ca, phosphorus (P), albumin, and 25-OH vitamin D were measured.

Chemiluminescent enzyme-labeled immunoradiometric assay and Siemens kit were used for serum PTH measurement (Immulite 2000 Systems Analyzers, UK) and normal levels were 11–67 pg/ml. 25-OH vitamin D was measured using chromsystems kits and HPLC method (Agilent 1200 series-Germany) and normal levels were 20–120 µg/l. In patients with normal serum Ca, P, and PTH levels, parathyroid pathology was excluded. Parathyroid sestamibi scintigraphy and/or neck magnetic resonance

imaging was performed in patients with high-normal Ca and inappropriately high-normal PTH levels. In patients with high serum Ca and PTH levels, 24-h urinary Ca was determined and renal US and bone mineral density were performed to screen for nephrolithiasis and osteoporosis. Parathyroid sestamibi scintigraphy was also used to confirm the localization of parathyroid pathology in these patients. Primary hyperparathyroidism (PHPT) was diagnosed when PTH levels were high in the setting of hypercalcemia and parathyroid lesion was detected in imaging techniques (US and/or parathyroid sestamibi scintigraphy). In all patients with suspected parathyroid lesion, also serum thyrotropin, serum-free triiodothyronine, serum-free thyroxine, anti-thyroid peroxidase antibody (antiTPOAb, normal range, <5.61 IU/ml), and anti-thyroglobulin antibody (antiTgAb, normal range, <4.11 IU/ml) were measured. The thyroid antibody levels over the upper range were accepted as positive.

Surgery is indicated in patients with overt complications of PHPT (nephrolithiasis, nephrocalcinosis, severe bone diseases, fracture, and neuromuscular dysfunction). In patients with asymptomatic disease, operation indications are defined as serum Ca concentration above 1 mg/dl above accepted normal range, 24-h urinary Ca excretion of more than 400 mg/day, creatinine clearance reduced by 30 %, bone mineral density t score lower than –2.5, and age under 50 [6]. Primary hyperparathyroidism patients meeting criteria underwent parathyroidectomy.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL, United States). Descriptive statistics were demonstrated as mean \pm standard deviation for continuous variables and as number of cases and (%) for nominal variables. The differences between independent groups regarding for continuous variables were evaluated by Student's *t* test or Mann–Whitney *U* test, where it is applicable. Chi-square test was used to investigate the difference between the groups regarding the categorical variables. A *P* value less than 0.05 was considered to indicate statistical significance.

Results

During the study period from August 2009 to January 2010, 6,528 patients underwent thyroid US in our clinic. There were 78 (1.19 %) patients with suspicious parathyroid lesion/lesions. 73 of these patients were female and 5 were male and mean age was 45.32 ± 12.59 . Lesions were located inferior or middle to right thyroid lobe in 25 (32 %) patients and located inferior or middle to left thyroid lobe in 43 (55.2 %) patients. In 10 (12.8 %) patients, bilateral suspected parathyroid lesions were observed. Mean

diameter of suspected parathyroid adenomas was 10.66 ± 5.22 mm (5.6–38.2 mm).

After laboratory examinations and imaging procedures, the diagnosis of a true parathyroid adenoma was made in 6 (7.69 %) patients (5 female and 1 male). Parathyroid scintigraphy was positive in 4 of these patients. Patients with true adenoma underwent parathyroidectomy and an adenoma was confirmed histopathologically also. In the remaining 72 patients (68 female, 4 male), US finding of a parathyroid lesion was accepted to be false positive. Among these, five patients with high–normal serum Ca and inappropriately high–normal serum PTH were evaluated with parathyroid sestamibi scintigraphy and/or neck magnetic resonance imaging and no pathology was detected. In follow up, serum PTH and Ca were normal in these patients. Also, there were 10 patients with low normal Ca, high PTH, and low 25-OH vitamin D. Serum PTH also normalized after administration of vitamin D in these patients. In the other 57 patients, a true adenoma was excluded by normal serum Ca and PTH levels.

Some demographic, clinical, and laboratory findings of patients with true adenoma and false positive lesions are given in Table 1. Mean age of patients with true adenoma

was 48.17 ± 5.27 and mean age of patients with false positive adenoma was 45.08 ± 13.01 ($P = 0.568$). Mean serum Ca, P, PTH, and 25-OH vitamin D levels were 10.57 ± 0.48 mg/dl, 3.03 ± 0.52 mg/dl, 182.91 ± 46.62 pg/ml, and 17.7 ± 9.31 µg/l, respectively, in patients with true adenoma. In patients with a false positive parathyroid lesion, serum Ca was 9.30 ± 0.44 mg/dl, P was 3.53 ± 0.56 mg/dl, PTH was 67.68 ± 37.63 pg/ml, and 25-OH vitamin D was 10.8 ± 6.2 µg/l (Table 1). The diameter of lesion was significantly higher in true adenomas compared to false positive lesions (15.80 ± 9.40 vs. 10.23 ± 4.57 mm, $P = 0.011$).

Among 72 patients with false positive parathyroid lesion, anti-TPOAb was positive in 50 (69.4 %), anti-TgAb was positive in 46 (63.9 %), and one of these antibodies were positive in 59 (81.9 %) patients. Forty-six (63.9 %) patients with a false positive lesion had thyroid dysfunction, 43 had hypothyroidism, and 3 had thyrotoxicosis. Ultrasonographically, 39 (54.2 %) patients had chronic thyroiditis alone, 20 (27.8 %) had chronic thyroiditis accompanied by multinodular goiter, 7 (9.7 %) had normal thyroid gland, and 6 (8.3 %) patients had multinodular goiter. Thus, 59 (81.9 %) patients with false positive parathyroid lesion had chronic thyroiditis ultrasonographically.

Table 1 Some demographical, clinical, and laboratory findings in patients with true parathyroid adenoma and false positive lesions

	False positive parathyroid lesions ($n = 72$)	True parathyroid adenomas ($n = 6$)	P
Age	45.08 ± 13.01	48.17 ± 5.27	0.568
Sex (female/male)	68/4	5/1	0.286
Serum calcium (8.6–10.2 mg/dl)	9.30 ± 0.44	10.57 ± 0.48	<0.001
Serum phosphorus (3.5–4.5 mg/dl)	3.53 ± 0.56	3.03 ± 0.52	0.038
Serum parathyroid hormone (11–67 pg/ml)	67.68 ± 37.63	182.91 ± 46.62	<0.001
25-OH vitamin D (20–120 µg/l)	17.7 ± 9.31	10.8 ± 6.2	0.078
Location of lesion			
Right inferior/middle	23 (31.9 %)	2 (33.3 %)	0.608
Left inferior/middle	39 (54.2 %)	4 (66.7 %)	
Bilateral	10 (13.9 %)	–	
Diameter of lesion (mm)	10.23 ± 4.57	15.80 ± 9.40	0.011
Positive anti-TPOAb	50 (69.4 %)	3 (50 %)	0.327
Positive anti-TgAb	46 (63.9 %)	2 (33.3 %)	0.139
Positive anti-TPOAb or anti-TgAb	59 (81.9 %)	3 (50 %)	0.063
Thyroid functions			
Euthyroid	26 (36.1 %)	3 (50 %)	0.731
Hypothyroid	43 (59.7 %)	3 (50 %)	
Thyrotoxicosis	3 (4.2 %)	–	
Ultrasonography findings			
Normal	7 (9.7 %)	2 (33.3 %)	0.196
Chronic thyroiditis	39 (54.1 %)	1 (16.7 %)	
Multinodular goiter	6 (8.4 %)	1 (16.7 %)	
Chronic thyroiditis and multinodular goiter	20 (27.8 %)	2 (33.3 %)	

anti-TPOAb anti thyroid peroxidase antibody, *anti-TgAb* anti-thyroglobulin antibody

AntiTPOAb was found to be positive in 3 (50 %) patients with true parathyroid adenoma and 2 (33.3 %) of these also had positive antiTgAb. Among patients with true parathyroid adenoma, 3 (50 %) had hypothyroidism and the other 3 (50 %) were euthyroid. In thyroid US, there was chronic thyroiditis in 1, multinodular goiter in 1, chronic thyroiditis accompanied by multinodular goiter in 2, and normal findings in 2 patients.

Discussion

Parathyroid incidentalomas in the literature are mostly reported to be discovered during thyroid surgery. Carnaille et al. [1] found incidental parathyroid lesions in 28 (0.6 %) of 4,697 normocalcemic patients operated for thyroid disease during a study period of 6 years. In another study, parathyroid glands were examined during thyroid operations in over 800 patients and additional parathyroid operations were performed due to abnormal appearing of parathyroid glands in 36 patients [7]. Since most of these patients were normocalcemic preoperatively, the authors concluded that parathyroid glands should also be examined carefully during thyroid operations even in patients with preoperative normal Ca levels. Two studies have compared clinical, biochemical, and pathological findings of patients with incidentally detected parathyroid lesions during operation and patients with preoperatively proven hyperparathyroidism [1, 2]. Both have reported that sex, number of diseased glands, and cell type were similar between the two groups. However, patients with incidentally detected parathyroid lesions during surgery were younger and had lower serum Ca and PTH levels compared to patients with known hyperparathyroidism. The authors suggested that incidentally detected parathyroid glands are mildly hyperfunctioning at the time of surgery and may represent an early stage of the disease. Previous studies recommend removal of an incidentally detected enlarged parathyroid gland during surgery because of the possibility for the eventual development of clinical true hyperparathyroidism and low incidence of permanent hypoparathyroidism in these cases [1, 8].

Ultrasonographically detected parathyroid incidentalomas are infrequently reported in the literature. In the largest series by Kwak et al. [4], among 6,469 patients examined by US, 112 (1.7 %) patients underwent PTH analysis in the washouts of FNAB due to suspicious parathyroid nodules. Parathyroid incidentalomas were identified in 14 patients based on pathology and 10 patients based on elevated FNA-PTH, resulting with a prevalence of parathyroid incidentaloma as 0.4 %. In another study, US showed suspicious parathyroid lesions in 38 (2.2 %) of 1,686 patients and 9 (0.53 %) were proven to be functioning

parathyroid tumors after measurement of PTH in FNAB washouts and cytological examination. However, serum Ca and PTH were high only in 5 of these patients and parathyroid pathology was not confirmed histopathologically in all patients [5]. Apart from these, there are a few case reports defining incidentally found parathyroid pathologies during US in the literature [9, 10]. In our study, prevalence of true parathyroid adenoma detected incidentally during US was 0.09 % in patients referred for thyroid US. This was lower than reported in previous few studies investigating parathyroid incidentalomas. One of the reasons for this may be that we have confirmed parathyroid pathology histopathologically in all patients in contrast to previous studies. There is evidence that thyroid nodules are found with a high prevalence (ranging from 24.7 to 51 %) in patients with parathyroid pathologies [11–13]. In the study by Kwak et al. [4], which found parathyroid incidentaloma prevalence as 0.4 %, the study group included patients referred for US guided FNAB of suspected thyroid nodules. Frasoldati et al. [5] reported ultrasonographically detected parathyroid incidentaloma prevalence as 0.53 %. However, their study group also consisted of patients with nodular goiter or autoimmune thyroiditis. This might have caused the high prevalence of parathyroid incidentalomas. However, we included all patients referred for thyroid US during the study period and US findings ranged from normal to chronic thyroiditis and nodular thyroid disease. In the study by Chen et al. [14], the records of 4,359 asymptomatic subjects who had undergone a health examination during a period of about 4.5 years in Taiwan were reviewed and hypercalcemia was found in 0.64 %, while PHPT was diagnosed in 0.092 % of the study group. This result was also consistent with our findings.

Mean age, sex distribution, and location of the suspected lesion were similar in true adenomas and false positive lesions in our study suggesting that these parameters cannot be helpful to discriminate suspected lesions. However, the ultrasonographically detected diameter of true parathyroid adenomas was significantly higher than false positive lesions. Our sample size is very small to determine a cut-off value that may indicate true adenoma; however, we think if suspected lesion is big in US, this should be taken in favor of true parathyroid adenoma.

Half of the patients with true adenoma in our study had positive thyroid antibodies. High prevalence of coexistent thyroiditis or thyroid nodules in patients with true parathyroid adenoma is not a surprising result. Depending on the method of examination, patient selection and surgical indications and procedure, coexistent thyroid pathologies in PHPT patients were reported to occur with a prevalence ranging from 17.8 to 84.3 % [15–18]. In a previous study, we have shown that 41.7 % of PHPT patients had

thyroiditis [19], which was higher than reported in different studies ranging from 3.8 to 10.9 % [16, 17, 20]. This was partly explained by moderate iodine deficiency in most of the regions of our country, implementation of iodization programme in 1999, routine measurement of Ca levels in patients admitting for thyroid disease, and evaluation of all PHPT patients with thyroid US in our clinic. The prevalence of positive thyroid autoantibody in patients with false positive lesion was 81.9 % in this study. Although not statistically significant, this was even higher compared to patients with true adenoma. Ultrasonographically detected chronic thyroiditis was also very high in patients with false positive lesion. Our results show that positive thyroid autoantibodies and the presence of chronic thyroiditis seem to be associated with interpretation of a lesion as parathyroid pathology incorrectly.

Level 6 (paratracheal) lymph nodes are observed with a high frequency in patients with chronic thyroiditis. In a study including 309 subjects, paratracheal lymph nodes were observed in 92.4 % of patients with autoimmune thyroiditis and 25.5 % of control group [21]. Also, number and diameter of lymph nodes were higher in autoimmune thyroiditis group. Most of the false positive lesions in our study were probably lymphadenopathies related to chronic thyroiditis.

The most important limitation of our study was that we could not identify these false positive lesions histopathologically. The reason for this was lack of any indication for surgery in these patients. Also, we did not evaluate these lesions cytologically and measure PTH and thyroglobulin levels in FNAB washouts. These interventions would help to detect the definite origins of most of these lesions. However, we excluded true adenomas in false positive lesion group with normal serum Ca and PTH levels in some patients, and normal imaging methods and normalization of high-normal serum Ca and high-normal PTH levels in follow-up in others. Another limitation of our study was that we did not compare the prevalence of positive thyroid antibodies and chronic thyroiditis in patients with and without suspicious parathyroid lesion.

In conclusion, US detected parathyroid incidentalomas are rare. However, we think examination of parathyroid lodges during routine thyroid US adds little time to the procedure and might be helpful to detect silent parathyroid pathologies in an early phase. Since clinically or ultrasonographically chronic thyroiditis is observed in majority of patients with false positive parathyroid lesion in US, more careful examination is required before further investigations in these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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