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Differentiated thyroid cancer in patients with prolactinoma

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Background/aim: Increasing evidence is available about the role of prolactin in the development of various cancers. The purpose of this study is to evaluate the frequency of thyroid cancer in patients with prolactinoma followed at a single site.

Materials and methods: The medical records of 182 patients diagnosed with prolactinoma were reviewed retrospectively. Serum prolactin, antithyroglobulin, antithyroid peroxidase antibody, thyroid-stimulating hormone, free T4, and free T3 values and pituitary gland magnetic resonance imaging and thyroid ultrasound reports were evaluated.

Results: Forty-five (39.5%) patients were found to have a thyroid nodule (13 solitary, 32 multiple). Ten patients were administered a thyroidectomy, and differentiated thyroid cancer (DTC) was detected in 6 of these patients (6/114, 5.3%). One patient had lung metastasis. The control group consisted of 113 individuals (101 females, 12 males with a mean age of 32.1 ± 9.1). In the ultrasound reports, 28 of these individuals (24.8%) had a thyroid nodule (5 solitary, 23 multiple), and one individual (1/113, 0.8%) had DTC.

Conclusion: When compared to the control group, thyroid volume and thyroid nodularity were significantly higher in patients with prolactinoma ($P < 0.001$, $P = 0.018$, respectively); however, no statistically significant difference existed for the incidence of thyroid cancer ($P = 0.196$).

Key words: Prolactinoma, thyroid cancer, prolactin, thyroid nodule, thyroid volume

1. Introduction

Prolactinomas are the most frequently observed secretory adenomas of the pituitary gland. They are characterized by an autonomous prolactin secretion formed by lactotrophic cells of the pituitary gland and compose approximately 40% of pituitary gland adenomas (1). Even though prolactin is a polypeptide, which is primarily secreted in the pituitary gland, it is also produced in various extrapituitary areas such as breast epithelial cells, the prostate, endothelium, skin, and immune system cells (2,3). The basic role of prolactin is to ensure breast growth and milk production. In addition to this, prolactin is a multipurpose hormone and cytokine, which also has a role in multiple biological functions such as reproduction, pregnancy, lactation, growth and development, metabolism, immune modulation, electrolyte transport, skin (integument) regulation, behavior, and carcinogenesis (2,4–6). Prolactin receptors are also present in peripheral organs such as the pituitary gland, the heart, the thymus, the uterus, and the adrenal gland (7).

The relationship between hyperprolactinemia and cancer has been a controversial issue of debate for a long period of time. Increasing evidence is available about the role of prolactin in cancers of various types, both reproductive and nonproductive, through its local production or accumulation. Prolactin may have a survival (antiapoptotic) effect or may act as a mitogen (8).

The frequency of thyroid cancer is not known in patients with prolactinoma. In this study, we aim to evaluate the frequency of thyroid nodules and thyroid cancer in prolactinoma by reviewing the data of 182 patients with prolactinoma who were followed at a single reference site for a period of 9 years.

2. Materials and methods

In this study, the medical records of 182 patients who applied to the Ankara Atatürk Training and Research Hospital Endocrinology Outpatient Clinic between January 2004 and June 2013 with medical issues such as infertility, menstrual irregularities (oligomenorrhea/amenorrhea), galactorrhea, hirsutism, and impotence and who were diagnosed with prolactinoma were reviewed retrospectively. One hundred and fourteen patients out of the above had an ultrasound (US) due to several

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reasons (such as the presence of a thyroid nodule in physical examination or because of impaired thyroid function tests). These individuals were included in the study. We calculated the estimated disease duration of our patients from the onset of symptoms such as amenorrhea and galactorrhea. All of the patients had an adenoma confirmed by pituitary gland magnetic resonance imaging (MRI). Adenoma sizes were grouped as microadenomas if they showed a size of ≤10 mm and macroadenomas if they showed a size of >10 mm. The control group was composed of 113 healthy individuals without any known prolactinoma, hyperprolactinemia, or thyroid disease.

For the US, an Esaote color Doppler US (MAG Technology Co., Ltd., Model: 796FDII, Yung-Ho City, Taipei, Taiwan) and its superficial probe (Model No: LA523 13-4, 5.5–12.5 MHz) were used. The thyroid volume was calculated for each lobe by an ellipsoid model formula (length × thickness × depth × 0.52). Patients who received radiotherapy for the head/neck region and/or surgical intervention were not included in the study. Approximately 1/3 of patients with acromegaly may have high prolactin levels (9). Therefore, patients with acromegaly were also not included. For patients with suspected acromegaly, serum IGF-1 levels and standard growth hormone response to the 75 g oral glucose tolerance test were checked. A fine-needle aspiration biopsy (FNAB) was performed for the patients from both the prolactinoma group and the control group, with thyroid nodules of sizes greater than 1 cm or less than 1 cm, having suspected sonographic characteristics. A goiter leading to compression symptoms, the presence of a toxic nodule, a multinodular goiter, and suspected malignancy in FNAB were indications of thyroidectomy. Following overnight fasting, the blood samples of patients were collected in the morning between 0800 and 1000 hours. Normal ranges of laboratory parameters evaluated in our study were thyroid-stimulating hormone (TSH): 0.27–4.2 IU/mL, free T3 (fT3): 2–4.4 pg/mL, free T4 (fT4): 0.9–1.7 ng/dL, antithyroid peroxidase antibody (anti-TPO): 0–35 IU/mL, antithyroglobulin (anti-TG): 0–40 IU/mL, prolactin in males: 3.46–22.4 ng/mL, and prolactin in females: 6–29.9 ng/mL.

Statistical analysis was performed with IBM SPSS Statistics 20 for Mac (IBM Corp., Armonk, NY, USA). Since the obtained data demonstrated normal distribution with the Shapiro–Wilk test, value comparisons between prolactinoma and control groups were performed with Student's t-test, and frequency comparisons between the two groups were performed with the chi-square test. The impact of the age variable on thyroid nodules, thyroid volume, and cancer was purified by a mixed model. The results were evaluated at a 95% confidence interval, and significance was assessed at $P < 0.05$.

3. Results

From the patients with prolactinoma, 103 patients (90.4%) were female, 11 patients (9.6%) were male, and the mean age was 35 ± 10.4 years (a range of 18–60 years). According to pituitary gland MRI results, 95 patients (83.3%) had microadenoma (mean adenoma size: 5 ± 1.9 mm) and 19 patients (16.7%) had macroadenoma (mean adenoma size: 20.4 ± 8.8 mm). In US, 45 patients (39.5%) had normal results, 45 patients (39.5%) had nodules (13 solitary, 32 multiple), and 24 patients (21.1%) had heterogeneity. The mean diameter of thyroid nodules was 12.3 ± 10.5 mm. In this group, the thyroid antibodies of 107 patients were checked. Seventeen patients (15.9%) were anti-TG positive, and 30 patients (28%) were anti-TPO positive. The thyroid volume calculated by US was 13.7 ± 7.2 mL.

When the patients with microadenoma were compared with the patients with macroadenoma, thyroid nodularity and thyroid cancer were reported at the same rates while thyroid volume showed an increase, at $P = 0.057$, $P = 0.797$, and $P < 0.001$, respectively.

Nineteen patients with nodules were administered FNAB. Out of these patients, 13 patients (68.5%) had benign nodules, 5 patients (26.2%) had nondiagnostic nodules, and 1 patient (5.3%) had a nodule with suspected malignancy. Ten patients were administered a thyroidectomy. Out of these, thyroid cancer was detected in 6 patients (5.3%). Two patients had papillary carcinoma, 2 patients had papillary microcarcinoma, and 1 patient had a concomitant presence of papillary carcinoma and follicular carcinoma. In addition, one patient had a concomitant presence of papillary microcarcinoma (at 3 foci) and a follicular variant of papillary cancer. All patients detected to have cancer were female and over 40 years of age. While the shortest period between prolactinoma diagnosis and thyroid cancer diagnosis was 0.5 years in these patients, the longest period was 6 years. One patient had lung metastasis, and this was the patient with the period of 6 years between prolactinoma diagnosis and thyroid cancer diagnosis (Table 1).

The control group was composed of 113 individuals. Of these, (89.4%) were female and 12 (10.6%) were male, and the mean age was 32 ± 9.1 years (a range of 18–56 years). In the thyroid USs, 57 individuals (50.4%) were normal, 28 individuals (24.8%) had nodules (5 solitary, 23 multiple), and 24 individuals (24.8%) had a heterogeneous appearance. The mean diameter of the thyroid nodules was 16.7 ± 11 mm. Twenty-five individuals (22.1%) were anti-TG positive and 27 individuals (23.9%) were anti-TPO positive. Thyroid volume calculated by US was 10.9 ± 2.2 mL. In this group, 9 individuals were administered a thyroidectomy, and 1 individual (0.8%) was detected to have papillary microcarcinoma. When compared to the control group, thyroid volume and thyroid nodularity

Table 1. Clinical characteristics of the patients with thyroid carcinoma.

No.	Age	Sex	Pituitary micro-/ macroadenoma	YD	Pathology	MC	RAI ablation	Clinical diagnosis	Met.	Stage
1	49	Female	Microadenoma	6	Papillary carcinoma	-	Yes	MNG	Lung	4c
2	44	Female	Microadenoma	4	Papillary microcarcinoma	-	Yes	MNG	None	1
3	42	Female	Microadenoma	3	Papillary carcinoma, follicular variant	+	Yes	MNG	None	1
4	40	Female	Macroadenoma	3	Papillary carcinoma	-	Yes	TNG	None	2
5	47	Female	Macroadenoma	2	Papillary carcinoma + follicular carcinoma	+	Yes	MNG	None	1
6	51	Female	Macroadenoma	0.5	Papillary microcarcinoma	-	Yes	TNG	None	1

MC: Multicentricity; Met.: metastasis; MNG: multinodular goiter; RAI: radioactive iodine; TNG: toxic nodular goiter; YD: year difference (interval between prolactinoma and diagnosis of thyroid cancer in years).

were significantly higher in patients with prolactinoma (P < 0.001, P = 0.018, respectively); however, no statistically significant difference was evident in terms of the incidence of thyroid cancer (P = 0.196). No significant difference was visible between the two groups in terms of thyroid antibody positivity and other characteristics evaluated (Table 2).

When the age effect was ruled out, the difference was observed as unaffected (P adj = 0.002) by age with regard to average volume between the patients with prolactinoma and the control group. As the age effect was once more ruled out in terms of thyroid cancer, statistical insignificance remained (P adj = 0.378).

Moreover, thyroid volume was higher in the prolactinoma group, and also in individuals with no concomitantly existing thyroid nodule, compared to control group patients (P = 0.005) (Table 3).

All prolactinoma patients detected to have cancer were administered radioactive iodine treatment. None of the patients followed at our site have died.

4. Discussion

Prolactin is primarily secreted from lactotrophic cells in the anterior pituitary gland, and it can also be produced in tissues such as the breast gland, immune system cells, the placenta, the prostate, and the brain. Prolactin may affect these tissues via autocrine/paracrine routes (10). The proliferative/antiapoptotic role of autocrine/paracrine prolactin has been confirmed by pharmacological approaches because it has been demonstrated that prolactin

Table 2. Clinical characteristics of the study population.

	Prolactinoma n: 114	Control n: 113	P
Age (years)	35.1 ± 10.4	32.1 ± 9.1	0.067 *
Sex (male/female)	11/103	12/101	0.809 **
Prolactin (ng/mL)	97.5 ± 65.1	11.9 ± 4.7	<0.001*
TSH (IU/mL)	2.2 ± 1.04	2.0 ± 0.8	0.122 *
fT4 (ng/dL)	1.3 ± 0.2	1.3 ± 0.2	0.174 *
fT3 (pg/mL)	3.3 ± 0.5	3.3 ± 0.4	0.531 *
Anti-TG positivity (%)	15.9	22.1	0.239 **
Anti-TPO positivity (%)	28	23.9	0.483 **

*: Difference between groups is tested via Student's t-test.
**: Frequency differences across groups are tested via chi-square test.

Table 3. Clinical characteristics of the study population.

	Prolactinoma n: 114	Control n: 113	P
US thyroid heterogeneity (%)	21	24.8	0.081**
Thyroid nodule (%)	39.5	24.8	0.018**
Thyroid volume (mL)	13.7 ± 7.2	11.0 ± 2.2	<0.001*
Thyroid volume in nodule-free patients (mL)	11.7 ± 4.2	10.3 ± 1.5	0.005*
Thyroid cancer rate (%)	5.3%	0.8%	0.196**

*: Difference between groups is tested via Student's t-test.
**: Frequency differences across groups are tested via chi-square test.

receptor (PRLR) antagonists partially inhibited growth in breast and prostate cancer cell cultures (11). The relationship between hyperprolactinemia and cancer is a controversial topic that has been debated frequently in recent years. Since the target tissue of prolactin is the breast, the breast has been used as a prototype in researching the tumor growth potential of prolactin. The proliferative effect of prolactin has been clearly revealed in vitro by breast tumor epithelial cultures derived from both mice and humans (12). Since the breast is the target tissue of prolactin, it may also contribute in its aberrant growth. The effects of prolactin and PRLR-altered expressions have been demonstrated in breast and other cancers (5). Nevertheless, the administration of these results in humans has always been questioned and debated. Studies demonstrating the relationship between increased prolactin levels and breast cancer are based on case reports, basic research, and epidemiological studies (13). Epidemiological studies conducted in the 1980s and 1990s have not been sufficient to establish the relationship between prolactin levels and breast cancer (5,11,14). Other tumor types may also be affected by prolactin. For example, it has been indicated in experimental studies that prolactin stimulates prostate cell proliferation and regulates prostate growth, and therefore theoretically affects prostate carcinogenesis (10,15). Prolactin is one of the cytokines with tropic effects on the prostate. In rodents, prolactin is involved in prostate organogenesis, secretory activity, and hyperplasia (8). In men, a slight correlation is present between hyperprolactinemia and prostate cancer risk. Nevertheless, an increasing amount of information suggests that prolactin produced by the prostate has a local effect (16).

Very few studies are present in the literature on the relationship between prolactin and thyroid cancer. In their study, Kedzia et al. demonstrated the presence of prolactin mRNA in thyroid and parathyroid tissues in wild-type mice for the first time. In that study, PRLR mRNA expression was demonstrated in both thyroid follicles and calcitonin-producing C cells (6). Lu et al. demonstrated in rats that hyperprolactinemia increased calcitonin release in thyroid C cells by the cAMP pathway with prolactin's indirect effect (17). Some authors have stated that prolactin had indirect effects on CD40 expression in thyrocytes by antagonizing modulator effects of IFN-γ and interleukin-4 (6). Costa et al. revealed for the first time PRLR expression in the human thyroid by reverse transcription polymerase chain reaction and immunohistochemical method. In that study, 93.3% of normal thyroid samples had PRLR expression, and 76.1% of tumors, irrespective of histological type, had a PRLR expression. In normal follicular or C cells, PRLR expression renders the thyroid a potential target for prolactin in physiological or pathological hyperprolactinemia (18).

In the population-based matched cohort study of 969 patients performed by Berinder et al. recently, a slightly increased overall cancer risk in patients with hyperprolactinemia was detected. This increased cancer risk was essentially attributed to upper gastrointestinal and hematopoietic cancers, an increased breast cancer risk for women was not found, and there was a reduced risk for prostate cancer in men (10).

Bhatavdekar et al. determined significant prolactin levels in patients with colorectal cancer (19). In their study, Soroush et al. detected prolactin elevation in 76.6% of patients with colorectal cancer and carcinoembryonic antigen (CEA) elevation in 59.6% of these patients, and they suggested that prolactin may be used as a better tumor marker in colorectal cancer patients compared to CEA (20). Some cancer types stated to have a potential prolactin effect on tumor development are hepatocellular carcinoma (21), malignant laryngeal tumors (22), tongue cancers (23), cervical cancers (5), ovarian cancers (24), and endometrial cancers (24). There have been studies indicating that prolactin is a valuable tumor marker, yet there have also been studies indicating the contrary (20).

In our study, the rate of thyroid cancer in patients with prolactinoma was 5.3%. All of the patients with thyroid cancer were female patients who were over 40 years old. Only 1 patient had suspected cancer, detected with presurgery FNAB, and other patients were operated on due to reasons such as toxic nodular goiter or multinodular goiter-forming compression symptoms. The shortest period between prolactinoma and thyroid cancer diagnosis was 0.5 years, and the longest period was 6 years (in the patient with lung metastasis). Normoprolactinemia was ensured in all patients with dopamine agonists (cabergoline and/or bromocriptine), and thyroid cancers were diagnosed in the follow-up process.

Moreover, thyroid nodule frequency and thyroid volume increased in patients with prolactinoma compared to the control group. However, no increase was observed in thyroid antibody positivity.

Sayki Arslan et al. reported that thyroid volume, thyroid autoimmunity, and thyroid nodule prevalence increased in patients with hyperprolactinemia (25).

Prolactin demonstrates its biological effects by interacting with PRLR. PRLR is a member of the hematopoietic cytokine receptor superfamily (18). Prolactin binding activates several signal pathways such as JAK/STAT (26,27), MAPK (12,26), and PI3K (5). The activation of these cascades results in differentiation, proliferation, survival, and secretion (5). Both animal studies and in vitro data reveal that prolactin contributes to tumorigenesis by promoting cell proliferation, increasing cell motility, and supporting tumor vascularization (28,29). Moreover, there is increasing evidence for locally (autocrine) produced prolactin's effectiveness in tumor growth rather than prolactin secreted from the pituitary gland because dopamine analogues cannot suppress prolactin production in extrapituitary areas (12). Normalization of prolactin with bromocriptine in metastatic breast cancer and prostate cancers has not apparently been beneficial in breast cancer (30) or prostate cancer patients (12).

In conclusion, the relationship between prolactin levels and the tumorigenic potential of prolactin (in several tumors) is controversial. According to our information, our study is the first to demonstrate the frequency of thyroid cancer in patients with prolactinoma. In our study, thyroid nodule frequency and thyroid volume have been found to increase in patients with prolactinoma compared to the control group. On the other hand, no significant increase was observed in the frequency of thyroid cancer. The number of operated cases in the prolactinoma and control groups was too low to assess the risk of thyroid cancer with hyperprolactinemia. Therefore, future studies done on a larger scale need to be conducted on this subject.

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