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Evaluation of the natural course of thyroid nodules in patients with acromegaly

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Abstract

Purpose To investigate the nodular thyroid disease (NTD) and the natural course of thyroid nodules in patients with acromegaly.

Methods 138 patients with acromegaly (73 F/65 M), whose initial thyroid ultrasonography performed in our university hospital, were included in this study. The frequencies of NTD, papillary thyroid cancer (PTC) and associated factors on nodule formation were investigated at initial assessment. Patients who had NTD continued to follow-up (n = 56) were re-evaluated with a ultrasonography performed after a mean 7-years follow-up period. The nodule size changes were compared with the initial data and the factors affecting nodule growth were investigated.

Results The frequency of NTD was found 69%. Patients with NTD were older (p = 0.05), with higher baseline IGF-1%ULN (upper limit of normal) (p = 0.01). In patients with NTD, the majority had similar nodule size (45%), decreased nodule size in 30% and nodule growth in 25%. In patients with active acromegaly at last visit, nodule growth was more significant (p < 0.001). For one unit change in the IGF-1 levels, nodule growth increased by 1.01 folds and presence of active acromegaly disease was related with ninefolds increase in nodule growth. The frequency of PTC was 14% in patients with nodule growth and PTC was diagnosed 11% of all acromegalic patients.

Conclusion Both NTD and nodule growth is more frequent in active acromegalic patients. Thyroid nodules may show dynamic changes according to the disease activity and nodule growth should be closely monitored due to the risk of malignancy in patients with active acromegaly disease.

Keywords Acromegaly · Thyroid nodule growth · Natural course · IGF-1 · Papillary thyroid carcinoma

Introduction

Acromegaly is a rare, multisystemic disease caused by growth hormone (GH) hypersecretion, and it may cause multiple comorbidities [1, 2]. The nodular thyroid disease (NTD) is one of the these comorbidities, which is as common as nearly 60% [3–11]. Associated factors on nodule formation are highly variable and the most common ones are the effects of GH and insulin-like growth factor-1 (IGF-1) [3–11]. In non-acromegalic patients, the most important factors on nodule development are iodine deficiency, nutritional goitrogens, radiation, smoking, age, sex and genetic background [12]. Thyroid nodules are common, but only 8–16% of them are malignant [13]. However, screening of papillary thyroid carcinoma (PTC) is recommended because of the increased frequency in patients with acromegaly [3–10, 14–18].

In non-acromegalic patients, there is variable data on the natural course of cytologically benign or ultrasonographically non-suspicious thyroid nodules [19–28]. Current guideline recommends serial ultrasonography (USG) and cytological evaluations in case of suspicious changes and increased nodule size [29]. However, there is only a few studies evaluating thyroid volume changes in acromegaly [11, 30, 31] and to the best of our knowledge, this is the first study that comprehensively evaluates the natural course of thyroid nodules in patients with acromegaly.

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In this study, we aimed to investigate the frequencies of NTD and PTC, along with associated factors on nodule formation in our acromegalic patient series. We also evaluated natural course of thyroid nodules and the relationship between nodule size changes and acromegaly disease activity.

Materials and methods

In this study, 138 patients with acromegaly (73 F/65 M) whose initial thyroid USG was performed in our university hospital at the time of acromegaly diagnosis were assessed retrospectively. The diagnosis of acromegaly was made according to the presence of typical clinical signs and symptoms, in accordance with the current guideline [1]. Magnetic resonance imaging of pituitary adenoma and laboratory tests yielding high IGF-1 levels compared to age-control matched normal levels and non-suppressible growth hormone (GH) levels as per oral glucose tolerance test (OGTT), were utilized to support acromegaly diagnosis.

Our study was performed in accordance with the Helsinki recommendations. Written informed consents were obtained from the participants, and the study was approved by the Ethics Committee of our university hospital.

Nodules detected only with thyroid palpation and without any radiological evidence were excluded. Radiologists experienced in sonography conducted the thyroid examinations using different sonographic devices (SI 400, Siemens, Erlangen, Germany; Logic 7, General Electric, Milwaukee, Wisconsin; Sonoline Antares, Siemens) with high-frequency (13 MHz) linear probes. NTD was determined using USG and a nodule was defined as an outgrowth exceeding 5 mm in diameter [32]. Pseudonodular images were excluded from this definition. Patients with at least one nodule, who met the criteria mentioned above, were confirmed to have NTD.

Dominant nodule size, the presence of single or multiple nodules, as well as USG features were evaluated. Fine-needle aspiration (FNA) was performed in nodules that were ≥ 1 cm or < 1 cm with suspicious features such as microcalcifications, irregular borders, hypoechogenicity, a length longer than width or absence of nodule halo. The nodules were classified as nondiagnostic (category 1, with same subsequent FNA results), benign (category 2), suspicious (category 3 and 4) or malignant (category 5 and 6) on the basis of at least one FNA, and according to the BETHESDA 2007 classification, because this is the classification that is valid for the period of study [33]. In patients with surgical intervention, thyroid surgery endications were evaluated. Patients with PTC in postsurgical pathology results were recorded.

Acromegalic patients with and without NTD were compared according to their sex, age at diagnosis, estimated duration of acromegaly, maximal tumor diameter, GH levels, IGF-1%ULN (corresponding to the percentage increase compared with the upper limit of normal), TSH levels (at the time of acromegaly diagnosis in the absence of central hypothyroidism), thyroid autoantibody positivity (TPOAb and/or TgAb positivity could be evaluated in 103 patients), presence of central hypothyroidism, glucose metabolism disorders [patients with diabetes mellitus (DM) or prediabetes], fasting plasma glucose (FPG) levels, HbA1c and homeostasis model assessment of insulin resistance (HOMA-IR) at initial assessment. Prediabetes was defined as impaired fasting glucose (IFG; FPG between 5.6 and 6.9 mmol/L) and/or impaired glucose tolerance (IGT; OGTT 2 h plasma glucose between 7.8 and 11 mmol/L) and/or HbA1c between 5.7 and 6.4%. DM was defined as FPG > 7 mmol/L, OGTT 2 h plasma glucose > 11.1 mmol/L and HbA1c > 6.4% [34]. The HOMA-IR was calculated with the formula: [fasting insulin (μU/mL) x FPG (mmol/L)] / 22.5. HOMA-IR values higher than 2.5 were used for indicating IR [35].

NTD patients who were not referred for surgery and who remained under surveillance (n = 56) were re-evaluated after a mean follow-up of 7 years between 2016 and 2017 years. The same experienced radiologist performed and compared the USG findings with the baseline results. American Thyroid Association (ATA) guideline was utilized both in nodule size calculation by baseline comparison and in evaluation of their frequencies [29]. Patients' nodules determined to decrease at least 20%, to have 0–20% dimensional changes and to increase 20% were denoted as nodule shrinkage, stable nodule and nodule growth, respectively. The patients with nodule growth were compared with patients who had stable nodule and had nodule shrinkage according to their sex, age at diagnosis, baseline GH levels, IGF-1%ULN, TSH levels, mean the time interval between two USG, GH ve IGF-1 levels at last visit, presence of LT4 replacement therapy for central hypothyroidism or primary hypothyroidism, and maximal thyroid nodule size, presence of single or multiple nodules and characteristical features of nodules. Acromegaly disease activity at last visit was evaluated according to current guideline and active disease is defined as high IGF-1 levels (adjusted to age and gender) with GH level > 1 ng/mL [1]. Cystic nodules were defined when fluid portion represented more than 50% of the volume of the lesion [36]. In patients with nodule growth, repeat FNA results were evaluated and PTC frequencies after thyroid surgery were also investigated. In addition, nodul size changes were compared between nodules which were initially < 1 cm or ≥ 1 cm.

Statistical analyses were performed using SPSS version 21.0. Categorical variables were presented as frequency and percentage, and numerical variables as mean ± standard deviation (SD). In dual independent group comparisons, Student's t-test was used for normally distributed numeric variables, and the Mann–Whitney U test was used for

non-normally distributed data. Categorical variables were compared using the Chi square test. Statistically significant results were defined with a p value of <0.05. The predictors of presence of NTD and thyroid nodule growth were assessed by a binary logistic regression analysis. Variables that have a p value of <0.05 in univariate analysis were included in the single variable predictive model.

Results

In initial evaluation, frequency of NTD was 69% (n = 95), mean dominant nodule size was 17.4 ± 9.7 mm and 19% of nodules (n = 18) were smaller than 1 cm. Patients with NTD were older (44 ± 13 & 40 ± 12; p = 0.05), baseline IGF-1%ULN were higher (p = 0.01). Baseline GH, TSH levels, frequency of thyroid autoantibody positivity, presence of central hypothyroidism and frequency of glucose metabolism disorders were similar (Table 1). Baseline IGF-1%ULN levels in patients with acromegaly that was statistically significant in univariate analysis was no longer significant with single variable predictive models.

Results of FNA (n = 55) were listed as benign (n = 39), suspicious for malignancy (n = 7), malignant (n = 6) and nondiagnostic (n = 3). The cause of thyroid surgery (n = 24) were listed as suspicion of malignancy (n = 10), progression in nodule size according to previous findings of acromegaly diagnosis (n = 8), presence of intratorasic goitre (n = 4) and thyrotoxicosis (n = 2) at initial assessment. PTC was diagnosed in 13 patients after thyroid surgery in these patients. PTC was detected in all patients who had suspicion for malignancy in preoperative FNA evaluation. In addition three PTC cases were found in patients who were operated with different endications.

Nodule size was stable in 25 (45%), decreased in 17 (30%) and increased in 14 (25%) out of 56 patients with NTD, who were re-evaluated with a repeat thyroid USG after a mean follow-up period of 88 ± 67 months. Nodule growth rates were similar, 27% (3 of 11) and 24% (11 of 45) in nodules which were <1 cm or ≥ 1 cm on initial evaluation, respectively. In patients with thyroid nodule growth, presence of

Table 1 Comparison of acromegalic patients with and without thyroid nodule in terms of baseline clinical and laboratory findings

N = 138	Patients with NTD (n = 95)	Patients without NTD (n = 43)	p
Age at diagnosis (years) Mean ± SD	44 ± 13	40 ± 12	**0.05**
Sex (F / M)	51 / 44	22 / 21	*NS*
Estimated duration of acromegaly (years) Mean ± SD	6.8 ± 4.9	5.6 ± 4	*NS*
Max. tumor diameter (mm) Mean ± SD	17 ± 11	19 ± 11	*NS*
Baseline IGF-1%ULN Mean ± SD	334 ± 149	254 ± 82	**0.01**
Baseline GH level (ng/ml) Mean ± SD	19 ± 17	19 ± 14	*NS*
Baseline TSH level (mIU/L) Mean ± SD	1.6 ± 2.2	1.9 ± 2.2	*NS*
Central hypothyroidism (n; %)	11 (12)	9 (21)	*NS*
Thyroid autoantibody positivity[a] (n; %)	14 of 72 (19)	7 of 31 (23)	*NS*
Glucose metabolism disorders[b] (n, %)	70 (74)	32 (74)	*NS*
Fasting plasma glucose (mg/dl) Mean ± SD	117 ± 40	119 ± 39	*NS*
HbA1c (%) Mean ± SD	7.1 ± 2.1	6.6 ± 1.7	*NS*
HOMA-IR Mean ± SD	4.5 ± 3.5	3.9 ± 2.4	*NS*

TSH level was assessed in patients without central hypothyroidism

NS not significant; *TSH* thyroid stimulating hormone; *HOMA-IR* homeostasis model assessment of insulin resistance; *IGF-1* insulin-like growth factor-1; *GH* growth hormone; *IGF-1% ULN* the % increase compared with the upper limit of normal, *NTD* nodular thyroid disease

$p<0.05$ statistically significant, Significant p values are shown in bold

[a]TPOAb and/or TgAb positivity could be evaluated in 103 patients

[b]Patients with diabetes mellitus or prediabetes

active acromegaly disease was more frequent ($p < 0.001$) and IGF-1 levels at last visit were higher ($p = 0.03$) than in patients without nodule growth. Age at diagnosis, sex, baseline IGF-1, GH, TSH levels, GH levels at last visit, presence of LT4 replacement, baseline maximal nodule size, presence of single or multiple, cystic and hypoechoic nodules were similar between the groups (Table 2).

In a logistic regression analysis using single variable predictive model for IGF-1 levels at last visit revealed an OR of 1.01 [$p = 0.022$; odds ratio (OR) = 1.011; 95% confidence interval (CI) = 1.001–1.019], according to this for one unit change in the IGF-1 levels, the odds of an nodule growth increases by 1.01. Presence of active acromegaly disease was related with 9.1 fold increase in the nodule growth ($p = 0.002$; OR = 9.0; 95% CI 2.011–35.129).

In patients without nodule growth, FNA was not repeated due to lack of suspicious findings. On the other hand, FNA was performed in 13 patients with nodule growth. In one patient FNA was not performed due to cardiac comorbidities and patient denial. PTC diagnosis was applied after thyroid surgery in two patients who were operated due to malignancy suspicion or nondiagnostic cytology. PTC frequency was 14% in patients with nodule growth.

Thus, PTC (n = 15) was diagnosed in 16% of acromegaly patients who had NTD and 11% of all acromegalic patients. All the patients who were diagnosed with PTC had a nodul size ≥ 1 cm in the baseline evaluation.

Discussion

In this study, we found the frequency of NTD in patients with acromegaly as 69% and these results are compatible with the previous results in the literature [3–11]. Although there was no control group in our study, it is known that the prevalence of sonographic nodule in our country is 23.5 and 37.4% between 18 and 65 years and above 65 years old, respectively [37]. While the increased frequency of NTD is well known in patients with acromegaly, various mechanisms have been proposed for nodule formation.

Table 2 Comparison of acromegalic patients with and without thyroid nodule growth in terms of clinical, laboratory and ultrasonographic findings

N = 56	Thyroid nodule without growth (n = 42)	Thyroid nodule growth (n = 14)	p
Age at diagnosis (years) Mean ± SD	44 ± 13	43 ± 13	*NS*
Sex (F / M)	24 / 18	7 / 7	*NS*
Baseline IGF-1%ULN Mean ± SD	318 ± 134	373 ± 187	*NS*
Baseline GH level (ng/ml) Mean ± SD	22 ± 18	21 ± 22	*NS*
Baseline TSH level[a] (mIU/L) Mean ± SD	1.5 ± 1	1.5 ± 0.7	*NS*
Thyroid autoantibody positivity[b] (n; %)	1 (7)	7 (16)	*NS*
The time interval between two USG (months) Mean ± SD	82 ± 69	108 ± 59	*NS*
Active acromegaly at last visit (n; %)	7 (17)	9 (64)	**< 0.001**
IGF-1 levels at last visit (ng/ml) Mean ± SD	185 ± 61	335 ± 356	**0.03**
GH levels at last visit (ng/ml) Mean ± SD	1.1 ± 1.3	2.5 ± 3.3	*NS*
Patients with LT4 replacement therapy (n; %)	10 (24)	7 (50)	*NS*
Baseline maximal nodul size (mm) Mean ± SD	16.1 ± 8.7	17.5 ± 9.7	*NS*
Baseline single nodule (n; %) / multiple nodules (n, %)	8 (19) / 34 (81)	1 (7) / 13 (93)	*NS*
Baseline hypoechoic nodule (n; %)	13 (30)	6 (43)	*NS*
Baseline cystic nodule (n; %)	14 (33)	5 (36)	*NS*

NS not significant; *TSH* thyroid stimulating hormone; *IGF-1* insulin-like growth factor-1; *GH* growth hormone; *IGF-1% ULN* the % increase compared with the upper limit of normal, *USG* ultrasonography, *LT4* levothyroxine

$p < 0.05$ statistically significant, Significant p values are shown in bold

[a]TSH level was assessed in patients without central hypothyroidism

[b]TPOAb and/or TgAb positivity could be evaluated in all patients

Most importantly, GH and IGF-1 have mitogenic and antiapoptotic effects, and IGF-1 has been shown to potentiate TSH-induced thyroid cellular growth in vitro studies [38]. It is also reported that the effects of IGF-1 receptor located on thyroid follicular cells are also responsible in cell proliferation due to autocrine and paracrine effects of IGF-1 [39, 40].

In this study, acromegalic patients with NTD were older than patients without NTD. It is well known that the incidence of NTD is increasing with age in non-acromegalic patients [12]. TSH levels were similar in our patients with and without nodules. Although high TSH levels are associated with increased prevalence of nodule development [41], nodule development in patients with acromegaly is previously reported to be independent of TSH [42]. Additionally, glucose metabolism disorders and IR have also reported to be associated with thyroid nodule development in some studies [43, 44]. The possible mechanism is explained with the interaction between the insulin pathway and the IGF-1 system leading to increased proliferation and differentiation in thyroid follicular cells [38]. However, in our study although IR was more frequent, there was no statistical significance in acromegalic patients with NTD.

Acromegalic patients with NTD had higher baseline IGF-1 levels in our series. This may be explained with proliferative and antiapoptotic effects of IGF-1 and has been reported similarly in previous studies [6, 11, 30]. On the other hand, there are also some studies that demonstrate contradicting results [3, 5, 7]. As it has been previously mentioned, the most important factors on nodule development in non-acromegalic patients, are iodine deficiency, nutritional goitrogens, radiation, smoking, sex and genetic background [12]. None of our patients had a history of neck irradiation and all patients were residing in areas with similar iodination status. The was no difference in sex between groups, however genetic background for thyroid disease and history of smoking were not evaluated in the retrospective part of our study due to missing data in some patients' files.

Although thyroid nodules are common and the majority are benign, they nevertheless require serial follow-up assessment [13]. When the growth or suspicious findings in thyroid nodules are observed, repeat FNA is suggested [29]. In several studies with non-acromegalic patients, natural course of thyroid nodules are evaluated [19–28]. According to the results of these studies, nodule sizes were stable in the majority during the follow-up period, while decreased nodule size was observed in a few studies. In these non-acromegalic patients, frequency of nodule growth was reported between 2.2 and 61.2% [19–27]. The reasons for this large range are probably related with varying number of patients and lengths of follow-up period in addition to the iodination status of the country that the study is conducted. Furthermore, criteria used for nodule size or volume increase were entirely different in these studies such as 15–50% [19–27]. However, in a recent study, there was no difference in malignancy between the cytological comparison of two different growth criteria (20 and 50%) [45].

In our study, we reported nodule growth in 25% of patients when we evaluated the nodule size based on 20% increase compared to baseline size according to the ATA guideline recommendation [29]. This ratio was similar with the two largest studies that were performed with non-acromegalic patients [26, 27]. Therefore, thyroid nodule growth in acromegalic patients may be similar with the general population. Another study from our country has also reported similar results in non-acromegalic patients [24]. There is no previous studies comprehensively evaluating the natural course of thyroid nodules in patients with acromegaly. However, a few studies with limited number of patients have demonstrated decreased thyroid volume and no significant change in the nodule sizes with successful acromegaly treatment [11, 30, 31]. To the best of our knowledge, this is the first study indicating that there is thyroid nodule growth in a quarter of acromegalic patients with NTD and this finding is similar with the general population.

Several parameters that may be associated with nodule growth such as age, sex, duration of follow-up, TSH levels, presence of single or multiple nodules, baseline nodule size, cystic component and echogenity were evaluated in non-acromegalic patients and different results were found [19–28]. While Durante et al. [27] reported that the presence of multiple nodules, baseline nodule volume and male sex were significantly associated with nodule growth, Kim et al. [26] reported that younger age, baseline nodule size over 1 cm, duration of follow-up longer than four years and presence of less cystic component were more important. Erdogan et al. [24] reported that the most important factor in predicting nodule growth was nodule hypoechogenity. In our study, nodule growth was significantly higher in patients with active acromegaly disease despite the similar follow-up periods; in other words similar duration of acromegaly disease. The groups consisted of patients in similar iodination areas, also TSH levels and frequency of thyroid antibody positivity were similar in the groups. IGF-1 levels were higher in acromegalic patients with NTD. Insistence of high IGF-1 levels probably also results with a cumulative effect on nodule growth. Therefore close monitoring of NTD is important in the surveillance of active acromegaly patients. In our study the odds of a nodule growth increased by 1.01 for one unit change in the IGF-1 levels and presence of active acromegaly disease was related with ninefolds increase in the nodule growth.

The most important concern in the follow-up of thyroid nodules that are considered initially as benign lesions with ultrasonographic or cytologic evaluation, is the risk of malignancy and this is most commonly associated with the increase in nodule size. Therefore FNA is recommended in

the presence of nodule growth more than 20% [29]. In a recent study, it has been shown that malign nodules grow more than 2 mm per year compared to benign nodules [46]. In our series, 13 of the 14 patients with nodule growth were recruited for FNA. A total of three patients underwent thyroidectomy, as a result of recurrent nondiagnostic outcomes or malignancy suspicious cytology in FNA, and PTC was detected in two patients. Although it is not possible to make precise interpretations due to low number of patients, in our series we found malignancy in 14% of patients with nodule growth. This frequency is quite high as in the three previous major studies evaluating non-acromegalic patients, PTC frequencies were reported to be as low as 0.3–2.4% in these studies [26, 27, 47]. Two of the patients with PTC were patients with active acromegaly disease. In a study comparing acromegalic PTC with non-acromegalic PTC, it is noted that hyperactive GH-IGF-1 axis may play a dominant role in the development of PTC rather than the *BRAF*V600E mutation [48].

In our acromegalic patient cohort, we found the prevalence of PTC detection as 11%. Unfortunately, the prevalence of thyroid cancer in the general population in our country is unknown. However, in a recent meta-analysis that included data from our country, PTC prevalence in patients with acromegaly was determined 4.3% [4]. In addition, in two studies conducted in our country, the incidence of PTC in patients with acromegaly was reported as 7.8% and 4.7% [5–17]. In this study we have found a relatively higher frequency and we think that this result may be explained with the addition of not only the baseline USG findings, but also the results from the follow-up thyroid USG findings.

The most important limitations of our study are the lack of a control group to compare thyroid nodule growth. However, the chance of comparison with many studies including a study from our country in the same subject and the sufficient numbers of acromegalic patients with and without nodule growth to compare in our own cohort alleviates this limitation. Since in this study was not a prospective study, a fixed standard follow-up protocol for thyroid nodules was not defined. However, demonstrating the relationship between acromegaly disease activity and nodule growth also increase the importance of our study.

In conclusion, frequency of NTD are increased and nodule development is most commonly associated with age and baseline IGF-1 levels in patients with acromegaly. Thyroid nodules may show dynamic changes according to acromegaly disease activity and that nodule growth should be closely monitored due to the risk of malignancy in patients with active acromegaly disease.

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Compliance with ethical standards

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

Ethical approval All procedures performed in this study involving human participants were approved by the institutional and/or national research ethics committee and complied with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine.

Informed consent Informed consent was obtained from all individual participants included in the study.

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