CLINICAL STUDY

Elastosonographic evaluation of thyroid nodules in acromegaly

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Abstract

Objective: Ultrasound-elastography (US-E) appears to be a helpful tool for the diagnosis of thyroid cancer. In acromegaly, the prevalence of thyroid cancer is still debated. The aims of this study were to evaluate thyroid nodules in acromegaly and to establish the accuracy of US-E in providing information on their nature, using cytological analysis as a reference.

Subjects and methods: US-E was applied to 90 nodules detected in 25 acromegalic patients and to 94 nodules found in 31 non-acromegalic goitrous subjects. The lesions were classified according to the elasticity scores (ES) as soft (ES 1–2) or hard (ES 3–4). Fine needle aspiration cytology could be performed in 60.8% of hard nodules in acromegalics and in 86.7% of hard nodules in controls.

Results: The prevalence of hard nodules was significantly higher in the whole group of acromegalic patients than in controls (56.8 vs 16.0%, $P < 0.0001$). The prevalence of hard nodules in patients with active acromegaly (68.9%) was greater, though not to a statistically significant extent, than that observed in cured (44.4%) and controlled (52.5%) patients. Cytology revealed malignancy or suspect malignancy in four of the nodules of non-acromegalic subjects and in none of the nodules of acromegalic patients.

Conclusions: This study has demonstrated a high prevalence of stiff thyroid nodules in acromegaly, greater than that found in non-acromegalic goitrous subjects. In acromegalics, hard nodules appeared not to be malignant on cytopathological examination and are probably of fibrous nature. Thus, US-E appears to be of limited value for the diagnosis of thyroid cancer in acromegaly.

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Introduction

Acromegaly is a slowly progressive disease caused by exaggerated GH secretion and characterized by several complications. Thyroid multinodular disease is a common finding in acromegaly (1–5). Functional, scintigraphic, and ultrasonographic features of acromegalic goiter have been largely investigated (3), but no data are available so far regarding the characteristics of thyroid nodules in acromegalic patients as provided by ultrasound-elastography (US-E). This new ultrasonographic dynamic technique has been likened to an 'electronic palpation' in that it provides an estimation of tissue stiffness (6, 7). The basic principle of US-E is that compression of the examined tissue produces a strain, which is smaller in hard tissues than in soft tissues. The results of this technique are scored by measuring the degree of distortion of the US beam under the application of an external force (6).

Malignant lesions are often characterized by greater stiffness than normal tissue (8), and US-E has been shown to be useful to differentiate cancers from benign lesions in prostate, breast, pancreas, and lymph nodes (9–11). Recently, US-E has been used to study the stiffness of thyroid nodules and has been proposed as the best available noninvasive tool for the diagnosis of thyroid cancer (12–18). However, no data are available at the moment on the use of US-E in evaluating thyroid nodules in acromegalic patients in whom the possibility of a higher incidence of thyroid cancer has been reported in some studies (19–21).

Aims of this study were to evaluate thyroid nodules in acromegalic patients by US-E and to assess the diagnostic accuracy of this technique in detecting thyroid cancer in this population.

Patients and methods

Subjects

Thirty-five consecutive acromegalic patients referred to the Division of Endocrinology of our Institution were studied. Diagnosis of acromegaly and definition of active disease were based on clinical signs, high baseline GH levels, lack of GH suppression below 1 μg/l after standard oral glucose load, and serum insulin-like growth factor 1 (IGF1) values increased above the normal range for age and gender (22). At diagnosis,

34 out of 35 patients displayed a pituitary adenoma (17 macroadenomas and 17 microadenomas) at magnetic resonance imaging.

Conventional preliminary US B-mode (US) and US color–power-Doppler were performed in all patients. US-E was also carried out in 31 non-acromegalic subjects (21 women and 10 men, mean age 58.1 ± 11.42 years) bearing nodular thyroid disease who served as controls. Ten acromegalic patients (five with normal thyroid gland, three with Hashimoto's thyroiditis, one with only cystic lesions, and one thyroidectomized for papillary carcinoma) were excluded from the study. US-E was performed in the other 25 patients (15 women and 10 men, mean age 57.2 ± 12.14 years), bearing at least one solid nodule. All patients and controls gave their informed consent to participate in the study, which was approved by the Ethics Committee of our Institute.

Ten patients presented active acromegaly according to the above mentioned criteria: two of them were newly diagnosed, three had previously undergone unsuccessful pituitary surgery (followed in one case by unsuccessful radiotherapy), and the remaining five were not controlled by medical treatment (somatostatin analogues associated in four cases to cabergoline), preceded in one case by unsuccessful radiotherapy. Seven patients had been cured from acromegaly by pituitary surgery only. The remaining eight patients were controlled by medical treatment (somatostatin analogues associated in two cases to cabergoline and in one case to pegvisomant): among these patients, five patients presented a history of pituitary surgery not followed by radiotherapy and one patient was treated by pituitary irradiation alone; for the remaining two patients, medical treatment had been chosen as primary therapy. All patients and controls were euthyroid and presented normal serum calcitonin levels.

Thyroid conventional US and US elastography

Thyroid US, US color–power-Doppler, and US-E were performed by the same endocrinologist skilled in thyroid US (M A), using a Hitachi Logos E, EUB 7500, (Esaote SpA, Genoa, Italy) and a 6–13 MHz linear probe. A careful examination of the following US parameters was performed on all thyroid nodules: nature, i.e. solid, liquid or mixed; echogenicity, i.e. hyperechoic, isoechoic or hypoechoic compared with normal parenchyma; margins, i.e. regular or irregular; size; homogeneity, i.e. homogeneous or inhomogeneous; spot calcifications, i.e. coarse or microcalcifications, these latter characterized by hyperechoic spots < 2 mm without acoustic shadowing; flow pattern, i.e. absence of blood flow (type I), perinodular and absent or slight intranodular blood flow (type II), marked intranodular and absent or slight perinodular flow (type III) (23).

Thyroid volume was calculated by the elliptical shape volume formula ($\pi/6 \times$ length $\times$ width $\times$ thickness) for each lobe (24). All solid nodules were examined by US-E. The principles of US-E consist of acquiring two ultrasonic images (before and after tissue compression with the probe) and tracking tissue displacement by assessing the propagation of the imaging beam. A dedicated software providing an accurate measurement of tissue distortion was used (combined autocorrelation method, provided by Hitachi Medical). The US elastogram was displayed over the B-mode image in a color scale depending on the magnitude of strain: red (soft tissue), green (intermediate degree of stiffness), and blue (hard, anelastic tissue). In order to classify the elasticity of the nodules, the color pattern of the thyroid lesion was evaluated by comparison with that of the surrounding tissue. Based on the overall pattern, the lesions were classified into four classes of hardness, i.e. elasticity scores (ES) (15, 16, 18, 25). ES 1 was assigned to nodules presenting elasticity in the whole examined area (the nodule is homogeneously green); ES 2 was assigned to nodules displaying elasticity in a large portion of the examined area (the nodule is green with some peripheral and/or central blue areas); ES 3 was assigned to nodules with stiffness in a large portion of the examined area (the nodule is blue with some peripheral and/or central green areas); ES 4 was assigned to anelastic nodules (the whole nodule is homogenously blue). To minimize the inter- and intraobserver variability, the freehand compression applied on the neck region was standardized by a real-time measurement displayed on a numeric scale (graded 1 to 5) and kept constant throughout the examination at an intermediate level optimal for US-E evaluation (from 3 to 4).

In order to obtain reliable elasticity images, the box was set on the nodule and attention was paid to include sufficient surrounding normal thyroid parenchyma. In evaluating mixed solid–cystic nodules, ES was attributed only to the solid component of the lesion. In nodules > 30 mm, we firstly studied the cranial portion of the lesion and then the caudal region, to avoid artifacts. Multiple frames were acquired and many elasticity images were generated; the best-fit B-mode sonogram–elastogram image pairs were used to assign the ES on the basis of the color scale. Images were also recorded to be reviewed by a second skilled US examiner (M M). The agreement on the scoring of US parameters was 90% between the two observers. In the remaining 10% of cases, the final score was agreed after conjoint reexamination of the recorded pictures.

Cytopathological diagnosis

Cytological examination of material obtained by fine needle aspiration cytology (FNAC) was used as reference standard to establish the benign/malignant nature of the lesion. Indeed, due to its high sensitivity and specificity, this technique is widely considered as the best single test for this differentiation.

FNAC was performed, under US guidance, using a 22-gauge needle attached to a 20-ml syringe. Adequacy of aspirates was defined according to the guidelines of the Papanicolaou Society (26). Criteria for establishing which nodule had to be aspirated were: a) simultaneous presence of at least two US patterns of malignancy, i.e. hypoechogenicity, irregular margins, intralesional vascularization, and spot microcalcifications, suggesting malignancy (23, 27, 28); b) US-E indicative of stiff nodule (ES 3 or 4); c) size > 6 mm. In patients with > 3 stiff nodules, only the most suspect lesions were submitted to FNAC.

In acromegalic patients, FNAC was performed in 31 (60.8%) of the hard lesions, namely 20 (54.1%) of the ES 3 nodules and 11 (78.6%) of the ES 4 nodules. FNAC was not carried out in 20 hard nodules: for 10 of these lesions (patients with multinodular disease in whom at least two suspect nodules had been recently aspirated), US characteristics of benignity (isoechogenicity, regular margins, type I or II flow pattern and absence of microcalcifications) were apparent. FNAC was not performed in another four nodules because of their small size, and in an additional six because of patients' refusal.

In non-acromegalic subjects, FNAC was performed in 13 (86.7%) of the hard lesions, namely six (85.7%) of the ES 3 nodules and seven (87.5%) of the ES 4 nodules.

All stiff nodules not undergoing FNAC were monitored by US and US-E for at least 12 months.

Statistical analysis

Continuous variables were expressed as mean $\pm$ S.E.M. Statistical analysis was performed using ANOVA or χ^2 test for quantitative and qualitative data respectively. A P value of < 0.05 was considered significant. Bonferroni correction was used for multiple comparisons with significance accepted at $P < 0.016$.

# Results

Thyroid conventional US and US elastography

In the 25 acromegalic patients enrolled in the study, the mean thyroid volume was 20.2 ± 9.41 ml (range 7.9–42.9), and 102 thyroid nodules were found, with the number of lesions in a single patient ranging from one to a maximum of 10. The mean size of the nodules was 10.7 ± 6.21 mm (range 2–39).

At US examination, 87 nodules (85.3%) were solid, four nodules (3.9%) were mixed, and 11 nodules (10.8%) were cystic. Sixty-five nodules (63.7%) were hypoechoic, 11 (10.9%) were isoechoic, 2 (1.8%) were hyperechoic, 13 (12.7%) were hypoisoechoic, and 11 (10.9%) were anechoic. Sixty-four nodules (62.7%) were homogeneous and 38 (37.3%) were inhomogeneous. Margins were regular in 80 nodules (78.4%) and irregular in the other 22 nodules (21.6%). Calcifications were found in seven nodules (6.8%) with microcalcifications in three cases (2.9%) and coarse calcifications in the remaining four cases (3.9%). At US color–power-Doppler examination, 58 nodules (56.8%) displayed type I flow, 33 nodules (32.4%) displayed type II flow, and 11 nodules (10.8%) displayed type III flow.

In acromegalic patients, excluding 11 cystic nodules and one completely calcific lesion, US-E examination was performed in 90 nodules, of which 18 were in cured patients, 40 in pharmacologically controlled patients, and 32 in patients with active disease. In all, 39 soft nodules and 51 hard nodules were found. In detail, the ES was 1 for 13 nodules (14.4%), 2 for 26 lesions (28.8%), 3 for 37 nodules (41.3%), and 4 for the remaining 14 (15.5%). The main conventional ultrasonographic features suggesting malignancy of the nodules characterized by ES 3 and 4 are shown in Fig. 1; with the exception of hypoechogenicity, the other parameters (inhomogeneity, irregular margins, intralesional vascularization and microcalcifications) were present in a minority of the stiff nodules. One such nodule is shown in Fig. 2.

The prevalence of different ES according to the activity of acromegaly is shown in Table 1. While in cured and controlled patients, the prevalence of hard nodules (ES 3–4) was similar to that of soft nodules (ES 1–2); in patients with active disease, hard lesions were highly frequent. In addition, the prevalence of hard nodules in patients with active acromegaly was greater (68.9%), although not attaining statistical significance ($P = 0.09$), than that observed in cured (44.4%) and controlled (52.5%) patients.

In a patient who had previously undergone radiometabolic therapy for hyperthyroidism seven nodules were found, of which five were hard lesions (ES 3 for three nodules and ES 4 for the other two nodules).
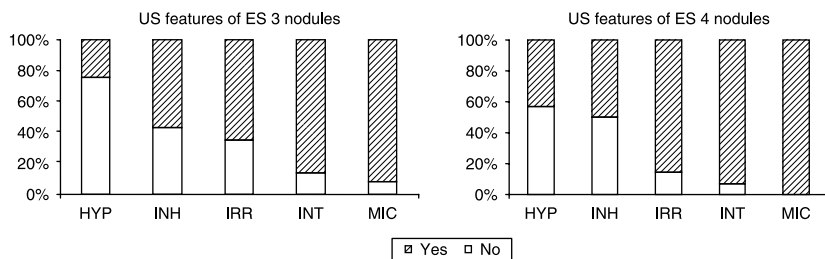
Figure 1 Prevalence of the main conventional ultrasonographic features suggesting malignancy among ES 3 and ES 4 nodules in acromegalic patients. HYP, hypoechogenicity; INH, inhomogeneity; IRR, irregular margins; INT, intralesional vascularization; MIC, microcalcifications.
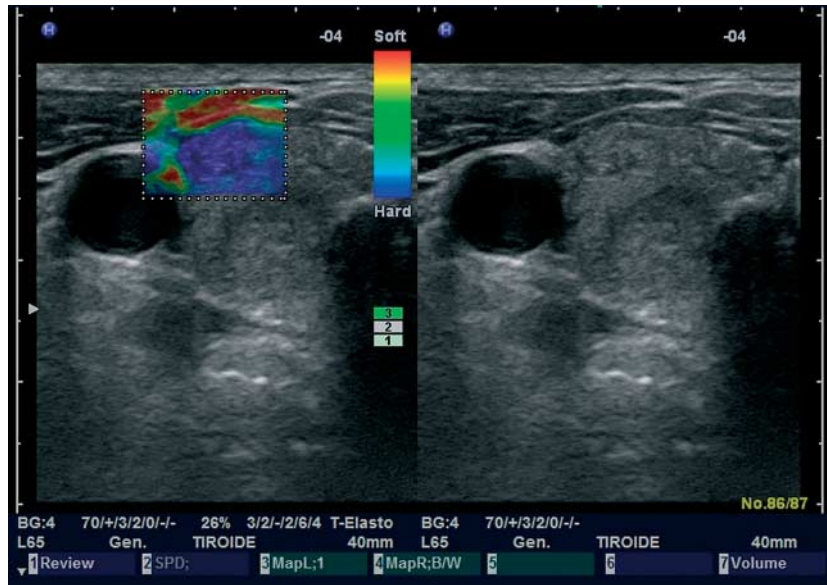
Figure 2 Conventional ultrasonographic (right) and elastographic (left) features of a hard, non-malignant (FNAC), thyroid nodule in a patient with acromegaly. The nodule was solid, hypoisoechoic, homogeneous, with regular margins and perinodular type II blood flow (not shown in the figure) at US evaluation. The whole nodule was homogenously blue at US-E evaluation, and according to the criteria mentioned in the text, the lesion has been assigned an ES of 4.

In non-acromegalic goitrous patients, US-E examination was performed in 94 nodules. In all, 79 soft nodules and 15 hard lesions were found. In detail, the ES was 1 for 59 nodules (62.8%), 2 for 20 lesions (21.3%), 3 for seven nodules (7.4%) and 4 for the remaining eight (8.5%).

The prevalence of hard nodules (ES 3 and 4) was significantly higher in the whole group of acromegalic patients than in control subjects (56.8 vs 16.0%, χ^2 33.1, $P < 0.0001$) and the same held true when comparing the three subgroups of acromegalic patients with non-acromegalic goitrous subjects (active disease versus controls, 68.9 vs 16.0%, χ^2 32, $P < 0.0001$; controlled disease versus controls, 52.5 vs 16.0%, χ^2 19, $P < 0.0001$; cured disease versus controls, 44.4 vs 16.0%, χ^2 7.5, $P = 0.0061$; Fig. 3).

In the six patients treated with cabergoline at the moment of the study, the prevalence of hard nodules was similar (50%) to that found in patients not receiving dopamine agonists (55%). No changes in US and US-E characteristics were observed in stiff nodules that had not undergone FNAC throughout a 12-month period of observation.

Cytopathological diagnosis

All the 31 thyroid nodules that had undergone FNAC in acromegalic patients were negative for malignancy or suspect malignancy (follicular lesions). Among the 13 hard nodules undergone FNAC in non-acromegalic subjects, one was shown to be malignant and the other three were characterized by features of follicular lesion. FNAC yielded inadequate or non-diagnostic smears in one out of 44 procedures; in that single case, sampling was repeated.

Discussion

To the best of our knowledge, this is the first study investigating the ultrasonographic and elastographic features of thyroid nodules found in a population of acromegalic patients. By conventional US, thyroid nodules were demonstrated in 25 out of 35 acromegalic subjects, a figure in line with the prevalence reported in the literature (5). The major finding of our study is the high prevalence of hard nodules detected by US-E in acromegaly. The prevalence of stiff nodules (ES 3 and 4) in the whole group of acromegalic patients (56.8%) is significantly higher than the prevalence of stiff lesions, one of which was of malignant nature, that we found in a population of non-acromegalic goitrous subjects (16.0%). This finding is chiefly accounted for by the higher occurrence of hard nodules in patients with active acromegaly, while soft and hard lesions appear to be equally distributed in cured or controlled patients.

Table 1 Prevalence of different elastographic scores according to the activity of acromegaly.

Disease status	ES 1	ES 2	ES 3	ES 4	ES 1–2	ES 3–4
Cured	6 (33.3)	4 (22.3)	5 (27.7)	3 (16.7)	10 (55.6)	8 (44.4)
Controlled	4 (10.0)	15 (37.5)	16 (40.0)	5 (12.5)	19 (47.5)	21 (52.5)
Active	3 (9.3)	7 (21.8)	16 (50.0)	6 (18.9)	10 (31.1)	22 (68.9)

Absolute number of nodules and, in brackets, percent values are shown.
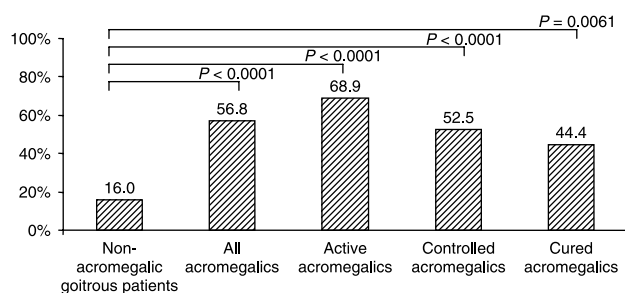
Figure 3 Prevalence of hard thyroid nodules at ultrasound-elastography in acromegalic patients in different stages of the disease and in non-acromegalic subjects with thyroid nodular disease.

However, the prevalence of hard lesions was also significantly higher in medically controlled and even surgically cured patients than control subjects, suggesting that cured patients may have developed stiff nodules during the active phase of disease. Of further interest, none of the 31 hard nodules detected in our acromegalic patients was malignant at cytological examination, while one out of 13 (7.7%) hard nodules aspirated in non-acromegalic goitrous subjects turned out to be malignant. The rate of malignancy in the hard nodules of our control population is lower than that reported by the literature (around 50%) (15, 18). Unfortunately, the three goitrous patients bearing follicular lesions on cytopathological examination have not undergone surgery so far, so that we lack histopathological information on the nature of their nodules. Were they malignant, the prevalence of carcinoma would rise in our series up to 30%, a figure more similar to that reported by other groups.

US-E, a procedure recently validated for the assessment of tissue elasticity (6), is currently considered a useful tool in the differential diagnosis of malignant lesions of prostate, breast, pancreas, and lymph nodes (9–11). Owing to the suboptimal diagnostic accuracy of conventional US in differentiating between benign and malignant nodules (27–29), US-E has been introduced in the evaluation of suspect thyroid lesions (12–18). Based on the greater degree of hardness of thyroid malignant nodules in comparison with benign lesions, US-E has proved effective in the identification of patients at high risk of malignancy with high sensitivity (82–97%) and specificity (81–100%) (12, 13, 15), although a lower accuracy was found for the detection of follicular thyroid carcinoma (15, 17).

In acromegaly, nodular thyroid disease is very common (1–4) likely as a consequence of chronically elevated levels of IGF1, a potent thyroid growth factor (1, 2). However, an increase in the prevalence of malignant thyroid nodules in acromegalic patients is still a matter of debate (5, 19, 20).

So far, studies applying US-E to the evaluation of thyroid nodules have been performed in non-acromegalic patients bearing single or multiple lesions for which surgery had already been planned because of large nodular size or suspicion of malignancy at FNAC (12, 13). Likely due to these selection criteria, the prevalence of hard nodules in these studies (33%) was higher than that found in our non-acromegalic goitrous patients. In other series, US-E has been used only for nodules larger than 10 mm (15).

In this study, US-E was applied to all of the nodules found in our population of acromegalic patients. At variance with findings in non-acromegalic subjects, where thyroid carcinomas could be detected with a great concordance between malignancy and hard elastographic pattern (12, 13, 15, 16, 18), in our acromegalic patients no suspect for malignancy was found at cytological examination in spite of the high frequency of stiff lesions.

Thus, in acromegaly, the hardness of the thyroid nodules at US-E does not seem to predict the malignant nature of the lesions. It is conceivable that a benign process, likely represented by nodular fibrosis, is responsible for the hard elastographic pattern of so many thyroid nodules in patients with acromegaly. Indeed, histologically proven fibrotic nodules of the thyroid appear to be characterized by a high stiffness index at US-E (17), and several hard nodules were detected in a patient of our series who had previously undergone radiometabolic treatment, which is known to induce fibrosis (30). Further, US-E is an appreciated tool to provide information about the degree of fibrosis in patients with liver cirrhosis (31).

GH and IGF1 are known to increase collagen synthesis and deposition (32), and their excess can induce fibrosis. This phenomenon might also contribute to the acromegalic cardiomyopathy (5). Fibrosis might also develop in the thyroid gland, justifying the greater prevalence of hard nodules in acromegalic than in non-acromegalic goiters. Along this line, the highest number of stiff lesions, twofold that of soft ones, was found in patients with active acromegaly, i.e. those with elevated GH and IGF1 serum levels.

In agreement with the lack of thyroid cancer in spite of prevalent hard nodules in the present series, the vast majority of the stiff nodules of our patients did not display conventional ultrasonographic features suggesting malignancy with the exception of hypoechogenicity, which, according to recent data (33), seems to be a typical feature of nodular fibrosis.

Cabergoline administration is known to induce cardiac, retroperitoneal, and possibly hypophyseal fibrosis. In our patients, the similar prevalence of hard nodules in subjects receiving and not receiving this drug does not support a role of this compound in the hypothesized fibrosis of thyroid nodules.

In conclusion, our study has demonstrated a high prevalence of hard thyroid nodules at US-E in acromegaly, particularly in active disease. Interestingly, none of the lesions turned out to be malignant at cytological examination. The hypothesis that nodular

fibrosis might account for this elastographic pattern is conceivable but needs histopathological confirmation. Thus, US-E appears to be of limited value for the detection of thyroid malignancies in acromegaly.

Declaration of interest

All authors declare that they have no conflict of interest.

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Author contribution statement

The first two authors contributed equally to the present manuscript.

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