RELATION BETWEEN QUANTITATIVE DESCRIPTION OF ULTRASONOGRAPHIC IMAGE AND CLINICAL AND LABORATORY FINDINGS IN LYMPHOCYTIC THYROIDITIS

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Objective. Relations between measurable properties of B-mode ultrasound images of thyroid gland and clinical and laboratory findings in patients with chronic inflammation of thyroid gland were studied.

Methods. Data from 65 patients with lymphocytic thyroiditis (LT) and 38 control subjects were analysed. Raw values of individual B-mode image pixels and standard co-occurrence second-order texture features were selected as quantitative image features. Thyroid antibodies, thyrotropin level, thyroxine replacement therapy, and body mass index were used as clinical variables.

Results. In the LT group, significant differences (t-tests, $p<0.05$) in image features were found for body mass indices (BMI) under and over 25 $kg.m^{-2}$, for thyroxine replacement therapy, and for the presence and absence of thyroid antibodies. Forward stepwise multiple regression was performed for the clinical or laboratory values as dependent variables and image features as independent variables. The following correlations were found: 1. between BMI and four image features in the normal group; 2. between the dose of thyroxine replacement therapy and two of image features in the LT group; and 3. for the level of thyroid antibodies in the LT group: five image features have correlated with the level of anti-thyroglobulin and three image features with level of anti-thyroperoxidase.

Conclusion. These findings suggest the possibility of using quantitative indicators of ultrasound image of thyroid gland as predictors of the presence or absence of thyroid antibodies in patient's blood or as an auxiliary tool for dose recommendation of thyroxine replacement therapy.

Key words: Thyroid gland – Lymphocytic thyroiditis – Ultrasound – Sonography – Image features – Texture analysis

Lymphocytic thyroiditis (LT), one of the most frequent thyroid disorders, is a chronic autoimmune inflammation of the thyroid gland (WARTOFSKY and INGBAR 1991). It usually results in hypothyroidism, which causes serious health problems to the patient. The structure of thyroid tissue is impaired by immune process. Such destruction may be either focal or, most frequently, diffuse. The tissue changes can be mostly detected by a routine method used in the diagnostics of thyroid diseases such as ultrasonography (BLUM et al. 1976, GOODING 1993, LOEVNER 1996). However, this disease can also be diagnosed by clinical examination, hormonal and immunological analyses of blood, and from cytological examination using fine needle aspiration biopsy.

Among the main advantages of sonographic imaging are its non-invasiveness, mobility, and low cost in comparison to other diagnostic imaging methods.

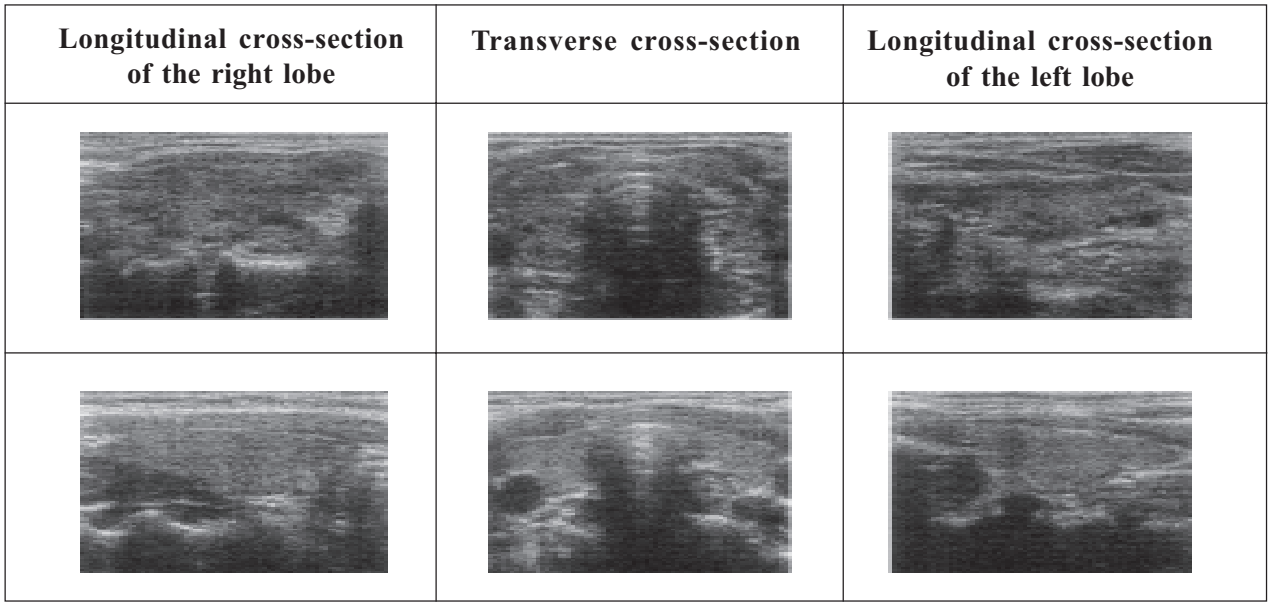

Fig 1 Sonographic images of lymphocytic thyroiditis (upper row) and (for comparison) of the normal thyroid gland (lower row). The gland in the longitudinal cross-sections is the area of uniform texture in the upper half of the image. In the transverse cross-section, it is the two-lobe formation similar to spectacles, also in the upper half of the image.

Apart from the measurement of thyroid gland volume and the detection of focal lesions like nodules or cysts, ultrasonography also contributes to the characterization of tissue echogenicity thus providing information about the follicular structure of the organ (Simeone et al. 1985, Solbiati et al. 1985). The examiner usually depicts the echogenicity of thyroid gland by comparing it with hyporeflective neck muscles (i.e., mm. sternothyroidei, mm. sternohyoidei, and mm. sternocleidomastoidei) without giving any quantifiable indices. Such subjectivity, depending only on the visual impression, experience, and judgement of the examiner, is a major disadvantage of sonographic imaging (Schiemann et al. 1999).

We have previously shown that the information related to diagnosis can be adequately extracted from sonographic images of thyroid gland and that it can be further used as quantitative (objective) indicators of sonographic examination (Smutek et al. 2001) or even for the automatic classification of thyroid inflammations (Smutek et al. 2000, Šára et al. 2001). In our forthcoming study (Smutek et al. 2003), which was performed in 100 subjects, the success of computer classification of LT from ultrasound images, tested by an independent test set, has achieved 100 % accuracy with sensitivity of 100 % and specificity of 88.9-100 %. For comparison the thyroid antibodies are positive in about 90 % of patients with LT (Blum 2001).

In this report we intend to point out the differences between ultrasound images of normal subjects and patients with thyroiditis and to find out whether there is a relation between the sonographic image of thyroid gland and clinical and laboratory findings, i.e., to prove or disprove the relation between quantitative indicators of ultrasound image and clinical parameters such as the level (or the presence) of specific antibodies, increased level of thyrotrophin, body mass index, and quantity of thyroxine replacement therapy.

Subjects and Methods

Subjects. Seventy patients (65 females, 5 males, aged between 18 and 74 years) with lymphocytic thyroiditis were included in our study. The patients were diagnosed by clinical examination, laboratory tests, and by fine-needle aspiration biopsy. At the time of image data acquisition 53 patients had been receiving thyroxine replacement therapy (dose between 50 and 150 μg/day), their thyrotrophin (TSH) levels varied up to 50.5 mU/l (56 patients were within the nor-

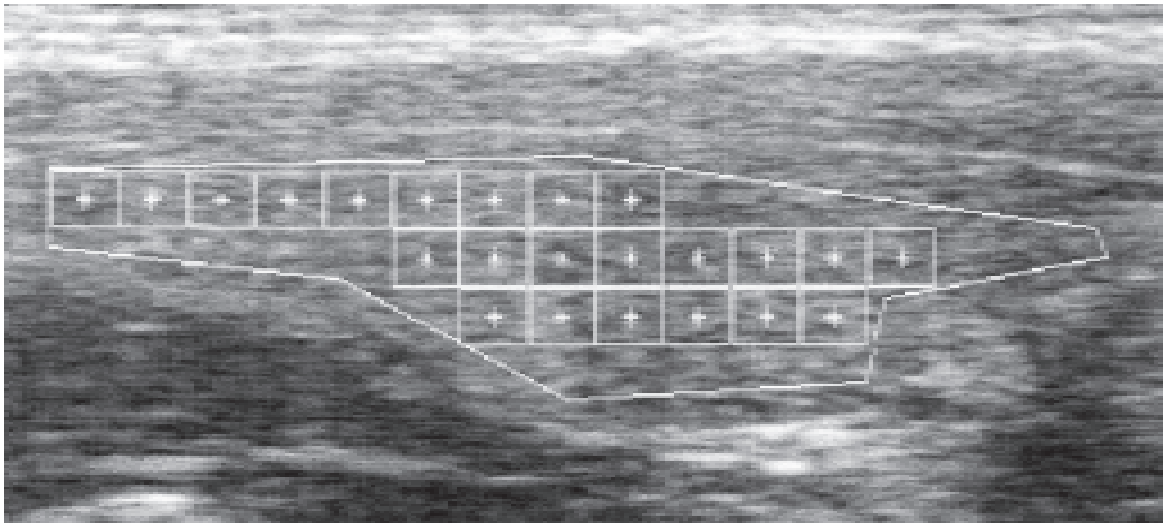

Fig 2 Sonographic image (longitudinal scan of right lobe) with drawn boundary of thyroid gland and texture samples (rectangular windows of 41x41 pixels).

mal range 0.5-6 mU/l), their level of thyroid antibodies varied between 0 and 6,000 kU/l in anti-thyroperoxidase (TPO) and 0 – 15,000 kU/l in anti-thyroglobulin (TGAB), 60 patients were positive for the presence of TPO and/or TGAB (TPO or TGAB values > 60 kU/l). Patients' body mass index (BMI) was between 17 and 41.3 $kg.m^{-2}$ (36 patients had excess weight, i.e., BMI > 25 $kg.m^{-2}$).

The patients were compared with 38 euthyroid volunteers (Normal) (33 females, 5 males) with homogeneous thyroid lobes of normal size. They had never undergone antithyroid drug or radioiodine treatment or thyroidectomy before and did not suffer from any other autoimmune disease. Volunteers' BMI was between 16.7 and 41.1 $kg.m^{-2}$ (10 volunteers had excess weight with BMI > 25 $kg.m^{-2}$).

Informed verbal consent was obtained from all participants and the procedures followed were in accordance with the ethical standards of our institution's committee on human experimentation.

Methods. Sonographic imaging system Toshiba ECCO-CEE (console model SSA-340A, Otawara, Tochigi 324, Japan) equipped with an 8-MHz linear transducer (model PLF-805ST), allowing a maximum depth of examination 40 mm, frame rate 19 Hz, was used. The RS170 output from the sonograph was digitized using Data Translation DT3155 frame-grabber (Data Translation, Inc., Marlboro, USA). B-mode images with an amplitude resolution of 8 bits, 415x381 pixels, as shown in Figure 1, were recorded.

In order to determine reproducible echo levels, constant sonographic operating conditions were defined. The following parameters (adjustable functions of the console, using manufacturer's terms for the functions) on the sonograph were fixed to the same values as when used for routine examination, i.e., a gain of 92, medium sensitivity by depth, maximal acoustic power, and maximum spatial resolution.

In order to include the sufficient amount of diagnostically relevant information, the scans were taken for several (10 for each lobe) transducer positions placed in parallel with each other and separated by arbitrary separations, within the range of 10 mm, according to the physician's decision. Only longitudinal cross-sections were used in our study, because they provide greater amount of image data from a larger contiguous area of the gland tissue (Sara et al. 2001).

The total number of sonographic images acquired was 2,160. MATLAB software (The MathWorks, Inc., Nattick, MA, USA) was then used to analyze the digitized images.

Since the changes of thyroid structure are mostly diffuse, it is possible to use global textural characteristics within the image region that corresponds to the thyroid gland tissue. An interactive MATLAB tool was used by a physician to roughly delineate the bound-

Table 1
Description of Haralick texture features (Haralick and Shapiro 1993) and their abbreviations used in the text

Abbrev.	Feature name	Definition
H1	Cluster tendency	$\sum_i \sum_j (i-\mu_i + j-\mu_j)^2 C_{\vec{d}}(i,j)$
H2	Texture entropy	$-\sum_i \sum_j C_{\vec{d}}(i,j) \log C_{\vec{d}}(i,j)$
H3	Texture contrast	$\sum_i \sum_j \lvert i-j \rvert C_{\vec{d}}(i,j)$
H4	Texture correlation	$\frac{\sum_i \sum_j (i-\mu_i)(j-\mu_j) C_{\vec{d}}(i,j)}{\sqrt{\text{var(i)var(j)}}}$
H5	Texture homogeneity	$\sum_i \sum_j \frac{C_{\vec{d}}(i,j)}{1+\lvert i-j \rvert}$
H6	Inverse difference moment	$\sum_{i,i\neq j} \sum_{j,i\neq j} \frac{C_{\vec{d}}(i,j)}{\lvert i-j \rvert}$
H7	Maximum probability	$\max_i \max_j C_{\vec{d}}(i,j)$
H8	Probability of run length of 2	$\sum_i \frac{(C_i - C_{\vec{d}}(i,i))^2 C_{\vec{d}}(i,i)}{(C_{\vec{d}}(i))^2}$
H9	Uniformity of energy	$\sum_i \sum_j (C_{\vec{d}}(i,j))^2$

where $\mu_i = \sum_i \sum_j i C_{\vec{d}}(i,j)$; $\mu_j = \sum_i \sum_j j C_{\vec{d}}(i,j)$; $C_i = \sum_j C_{\vec{d}}(i,j)$

$\text{var}(i) = \sum_i \sum_j (i-\mu_i)^2 C_{\vec{d}}(i,j)$; $\text{var}(j) = \sum_i \sum_j (j-\mu_j)^2 C_{\vec{d}}(i,j)$

$i, j = 0,1,\ldots, G-1$.

Given separation vector $\vec{d}$, $C_{\vec{d}}(i,j)$ is the co-occurrence matrix, i.e. the 2-dimensional histogram of simultaneous occurrence of values *i* and *j* in all image pixel pairs separated by $\vec{d}$.

ary of the gland and select the region, as illustrated by the outline in Figure 2.

As quantitative indicators of image (texture description) we used raw gray scale values of individual image pixels (RAW) and Haralick texture features (Haralick and Shapiro 1993) – see Table 1. Haralick texture features were computed from the co-occurrence matrix corresponding to a one-pixel separation in the direction of ultrasonic wave propagation ($\vec{d} = (1.0)$, see the definition in Table 1). The co-occurrence matrix, computed for 256 gray levels, was based on texture samples, which were defined as rectangular non-overlapping windows within the segmented boundaries, as illustrated in Figure 2. These features are of statistical nature and do not require any image pre-processing.

As the next step the mean values of all used features (RAW, H1, H2, H3, H4, H5, H6, H7, H8, H9) were calculated and assigned to each subject.

Statistical evaluation was performed using t-test for independent samples for detecting differences between the groups and forward stepwise multiple regression was carried out for evaluating the correlations between clinical, laboratory and ultrasound findings. The level of significance was taken at $p<0.05$.

Results

Significant differences between the LT and Normal groups were found in RAW, with $p<0.001$ (see Figure 3), H3 ($p<0.001$), H4 ($p<0.001$), H5 ($p<0.001$), H6 ($p=0.002$), H8 ($p=0.023$), and BMI ($p=0.01$).

Forward stepwise multiple regression was performed for BMI (dependent variable) and all image features, including gray scale values (independent variables) in both groups. In healthy individuals the correlation with multiple R-Square (coefficient of determination) 0.708 (F-test 16.98, $p<0.00001$) was detected. The BMI correlated with following image features: RAW (beta coefficient -0.82, $p=0.000036$), H1 (beta coefficient 4.55, $p=0.00067$), H4 (beta coefficient -1.71, $p=0.00012$), and H5 (beta coefficient 4.05, $p=0.000034$).

In LT group we found significant differences in image features RAW ($p=0.021$), H1 ($p=0.001$), H3 ($p=0.021$), H4 ($p=0.017$), H5 ($p=0.022$) for groups of subjects with BMI lower and higher (excess weight) than 25 $kg.m^{-2}$.

Furthermore, we were looking for differences between patients in the LT group with and without thyroxine replacement therapy. We found significant differences in image features RAW ($p=0.046$), H3 ($p=0.048$), and H6 ($p=0.001$).

Forward stepwise multiple regression was performed for dose of thyroxine replacement therapy in µg/day (dependent variable) and all image features (independent variables) in the LT group. Dose of thyroxine replacement correlated with image feature H4 (beta coefficient 0.25, $p=0.023$) and H6 (beta coefficient 0.53, $p=0.00005$). Multiple R-Square (coefficient of determination) for this correlation was 0.386 (F-test 17.92, $p<0.00001$).

In LT group we found significant differences in image features RAW ($p=0.003$), H3 ($p=0.021$), H4 ($p=0.034$), H5 ($p=0.021$) for groups of subjects with presence and absence of TPO or TGAB. The signif-

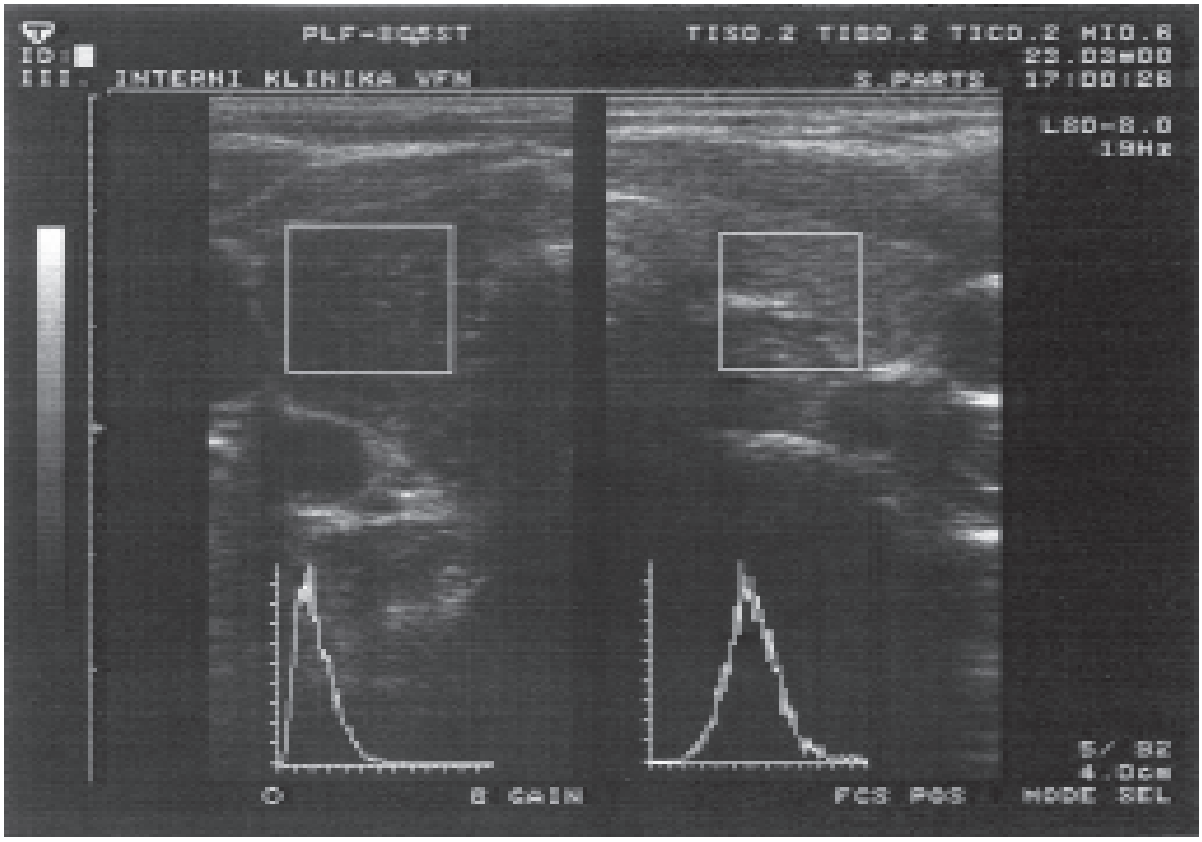

Fig 3 Comparison histograms of RAW values for single images. Transversal scan of right thyroid lobe from LT group (shown left), transversal scan of left thyroid lobe of Normal subject (shown right).

icant difference was also found in the dose of thyroxine replacement therapy (p=0.028).

Forward stepwise multiple regression was performed for TGAB and TPO (dependent variables) and all image features, including gray scale values (independent variables) in the LT group. We found correlation between level of TGAB and image features H1 (beta coefficient 1.51, p<0.00001), H4 (beta coefficient -1.29, p<0.00001), H5 (beta coefficient 1.76, p<0.00001), H7 (beta coefficient 11.67, p<0.00001), and H9 (beta coefficient -12.55, p<0.00001). Multiple R-Square of this correlation was 0.81 (F-test 23.2, p<0.00001).

The correlation for levels of TPO was weaker with coefficient of determination 0.67; F-test 17, p<0.00001. Levels of TPO correlated with image features H6 (beta coefficient 0.28, p=0.05), H7 (beta coefficient 11.11, p<0.00001), and H9 (beta coefficient -11.5, p<0.00001).

Discussion

The differences of image features (RAW, H3, H4, H5, H6, H8) between the LT and Normal groups suggest the possibility of using them as features for automatic discrimination between normal sonograms and sonograms with LT as in (Sara et al. 2000), for example.

The finding of correlation between BMI and image features in Normals suggests that there is a relationship between the ultrasound image of thyroid gland and the body weight. We did not find any similar correlation in persons with lymphocytic thyroiditis. It is not clear whether it is caused by pathologic changes prevailing in the ultrasound image (affecting the sonogram so much that the correlation is not detectable anymore) or whether the correlation disappearance is caused by LT in general.

In LT group the patients with weight excess had significantly different image features than patients with

normal weight. This suggests a possibility that the image features with the significant differences (RAW, H1, H3, H4, H5) could detect the underlying autoimmune processes in thyroid gland and a possible weight gain.

The differences we found in image features between the patients with and without thyroxine replacement therapy can be explained by the circumstance that patients with less damaged thyroid gland have sufficient own thyroxine production or the autoimmune process is not pronounced, so they do not need the thyroxine replacement therapy yet. As we succeeded in finding the correlation between the dose of thyroxine replacement therapy (in μg/day) and two of image features, we suggest the possibility of dose recommendation for thyroxine replacement therapy according to the actual thyroid gland image. This method could help to assess the dosage which is nowadays based mostly on the level of TSH, especially in situations where discrepancies between clinical and laboratory examinations are present. Long-term and directly aimed studies still have to be done to verify such possibility.

On the other hand, no detection of differences between patients with normal and elevated TSH in LT group can be explained by the fact that the level of TSH is usually high or oscillating only at the beginning of treatment and then it stabilizes at the level within normal limits (Feldkamp and Horster 1995). Only a few patients in our survey were newly diagnosed cases of LT.

RAW, H3, H4, H5 values in the thyroid sonogram either with or without the presence of thyroid antibodies are significantly different and therefore can be used as predictors of the presence or absence of anti-thyroglobulin and anti-thyroperoxidase antibodies. The difference was also found for the dose of thyroxine replacement therapy (the patients with positive level of antibodies have significantly higher dose and vice versa), which is in accordance with the fact that the patients with higher autoimmune activity usually need higher dosages of thyroxine.

We have found a rather strong correlation, coefficient of determination was 0.81, between the image features (namely cluster tendency H1, texture correlation H4, texture homogeneity H5, maximum probability H7, and uniformity of energy H9) and the level of anti-thyroglobulin. The level of anti-thyroperoxidase was also in correlation with three of image features, but the correlation was weaker (coefficient of determination 0.67).

Detection of antibodies and ultrasonographic examination form an pair of important methods for establishing lymphocytic thyroiditis diagnosis. Our experiment has shown that quantitative indicators of ultrasonographic examination of thyroid gland are in good correlation with the level of thyroid antibodies in patient's blood. We have shown that it is possible to use the quantitative indicators of ultrasonographic examination for prediction of presence or absence of thyroid antibodies. Nevertheless, these indicators, computed solely on the basis of ultrasound image of the thyroid gland, cannot be used reliably for medical purposes as a basis for the estimation of the level of antibodies. The level of antibodies can be checked at the beginning of the treatment and later only clinical check-ups and ultrasonographic examination can be used for patient's surveillance during the treatment. This approach could reduce the costs by replacing subsequent immunological assays examinations by ultrasound examination, which would be carried out anyway, while the information about antibodies, although only estimated, would be also available.

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