Intralobular thyroid regeneration: ultrasound signs

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Introduction

Ultrasound scan (ultrasound) allows the determination of the specific pattern of the thyroid gland changes in Hashimoto thyroiditis (HT) [1-4,etc.]. These ultrasound findings include local lesions, which are also known as micronodules or pseudonodules by specialists [5, 6]. These areas in the gland are moderately or significantly hypoechoic and are spherical or ellipsoidal in shape. They predominantly have a clear edge and lack microcalcifications. Moreover, they are located separately or in groups and are usually several millimeters in size [5, 7, 8].

These pseudonodules of the thyroid gland are aggregations of lymphocytes formed due to the replacement of follicular tissue in the lobules and/or lymphoid germinal centers [5, 9, 10]. They clearly differ from thyroid nodules; however, according to some authors, they require needle biopsy for discriminatory diagnosis against microcarcinomas [11]. Despite this precaution, experts assess this focal and diffuse process as highly sensitive and highly specific in Hashimoto thyroiditis ultrasound/sonoelastography diagnosis [7, 10].

In recent review articles and guidelines for ultrasound of the thyroid gland, this pseudonodulation process is merely considered as a symptom of Hashimoto thyroiditis, without explaining variants of its changes [12, 13]. Meanwhile, there are facts that significantly complement our knowledge about the pseudonodules of the thyroid gland, which reveal the patterns and essence of this process. The regeneration process is among them [14].

Terminology

Thirty years have passed since the first publication [for example, 2] on such changes in the thyroid gland and twenty-five years since the publication of the more detailed article by Yeh et al. about the kinds and characteristics of micronodules in Hashimoto thyroiditis [5]. Since then, the empirical terminology designating this phenomenon in the thyroid gland has been modified and complemented.

Terms such as “multiple hypoechoic foci or patches scattered throughout an otherwise normoechoic gland” [2], “micronodulation”, [2, 13, 15, 16] and “pseudonodulation” [6, 7, 10, 12, 17, 18] have been used. Along with these designations, experts offer additional empirical terms such as “Swiss cheese” [17], “honeycomb” [17], and “giraffe” [6, 8, 12] (despite the fact that the term “giraffe” was previously used by Bonavita et al. to designate another process related to true nodes in the thyroid gland [19]).

Some authors use the term “macronodules” for “focal lesions [?] 5 mm in diameter” to distinguish between small and large focal hypoechoic lesions in hypoechoic tumors [9]. Among all these variants, “pseudonodulation” has become the most commonly used term and “micronodulation” the less commonly used term.

The lobules with lymphocytes are known as the base of pseudonodules in HT [5]. Therefore, it is appropriate to call these masses by their own name and not by other terms. Otherwise, incorrect designations create notional difficulties: (i) “pseudonodules” are opposed to a completely different phenomenon — nodules,

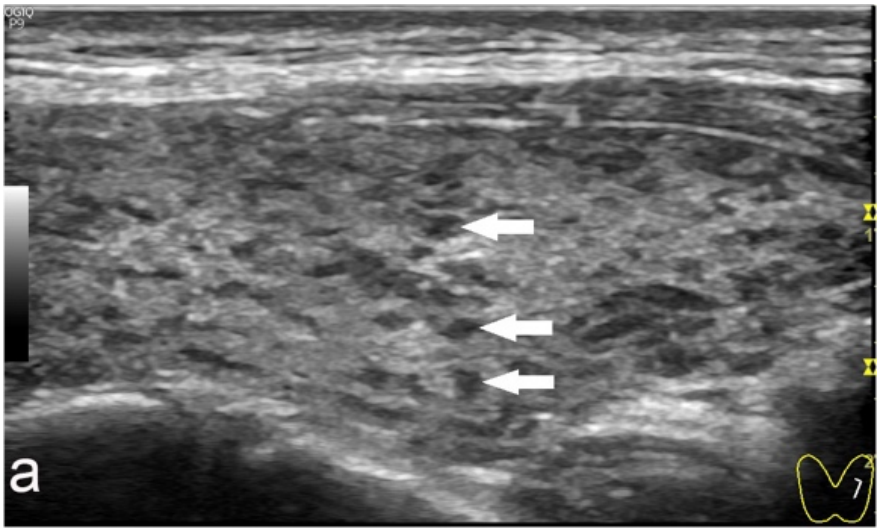
(ii) “micronodules” are confused with true small nodules, and (iii) empirical names (giraffe, Swiss cheese, honeycomb, etc.) distract us from understanding the essence of the process.

Hypoechoic lobules in HT are better designated as “lymphoid lobules”. This term contains the real semantic meaning of the process, shows the difference from any nodulation phenomenon, and at the same time puts in the picture the local characteristic of changes in the thyroid gland. In the further sections of this article, local hypoechoic areas characteristic of HT will be called lymphoid lobules.

Intralobular regeneration and its phases

Unlike nodules, which are characterized by staging, the destructive, lymphoid, and reparative processes in the lobules of the thyroid gland are marked by a change in phases. Staging is a unidirectional process that ends with the irreversible scarring of the tissue of a nodule, in the place of which a new nodule does not arise [20, 21, 22]. At the same time, the phasicity in the lobule represents a sequential and reversible phenomenon proceeding from the normal follicular structure to its destruction, utilization, replacement by lymphocytes, and further repair through regeneration [14].

Depletion and the subsequent destruction of follicles inside the lobule can result in minor lymphocytic infiltration, without significant lymphoid hyperplasia and hypertrophy of the lobule. With ultrasound, destruction and minor lymphoid intralobular infiltration are noticeable as a point element of moderate or significant hypoechogenicity in the lobule, which usually has a maximum size of 1.5–2 mm (Figure 1). This condition of the lobule, regardless of its size, refers to the**destruction phase** accompanied by lymphoid lesions.



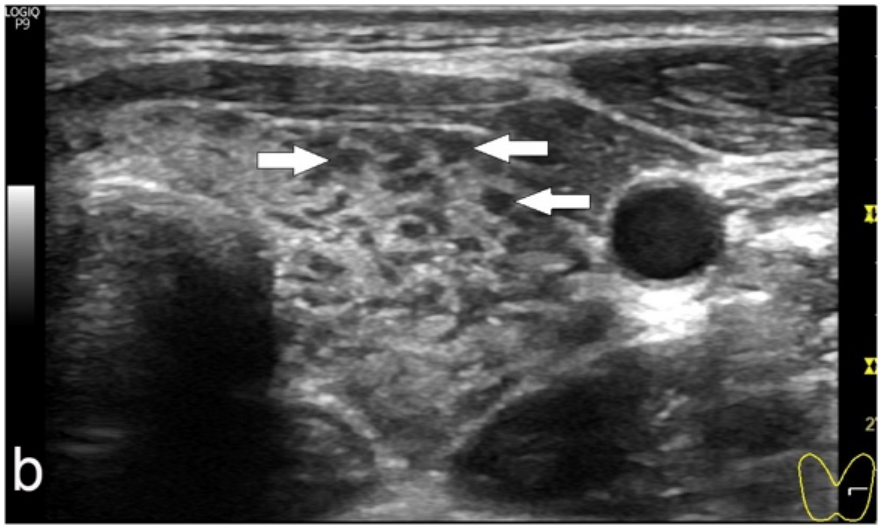
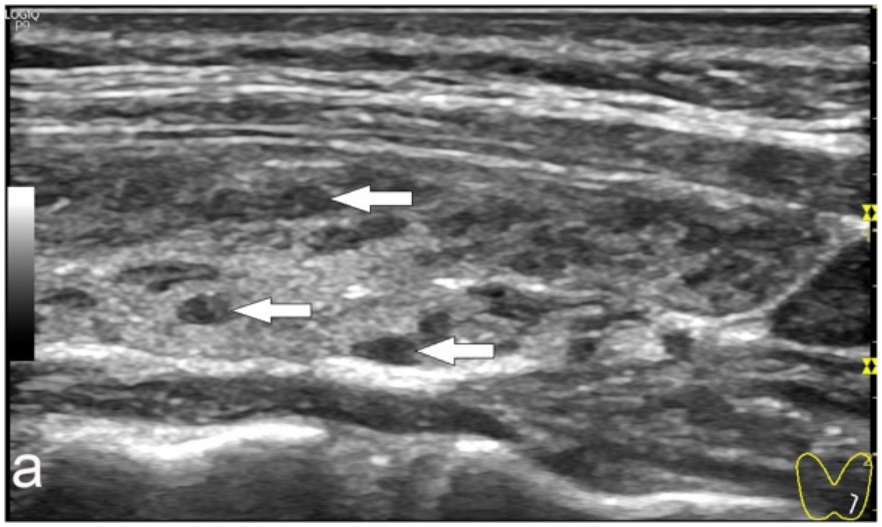


Figure 1. The left lobe of the thyroid gland (**A** is the transverse, and **B** is the longitudinal views) in a 22-year-old female patient (hypothyroidism – thyroid stimulating hormone (TSH) up to 10 μIU/ml, but replenished with levothyroxine up to euthyroidism; thyroid peroxidase antibodies (TPOAb) 500 [<5.6], thyroid globulin antibodies (TGAb) 20 IU/ml [<4.2]). Among the isoechoic tissues, several small, significantly hypoechoic inclusions in the lobules are visible (arrows). Destruction phase with lymphoid lesions.

In addition to minor lymphocytic infiltration, an active lymphocytic process with the formation of germinal centers and lymphoid hyperplasia can occur in the lobules, which leads to the hypertrophy of the lobule and the appearance of large lymphoid lobules. These changes are clearly visible with ultrasound as hypoechoic spherical or ovoid areas, a few millimeters in size, among the thyroid gland's isoechoic tissue. These are the areas that draw the attention of sonologists and are designated by them as "micronodules" and "pseudonodules" (Figure 2).



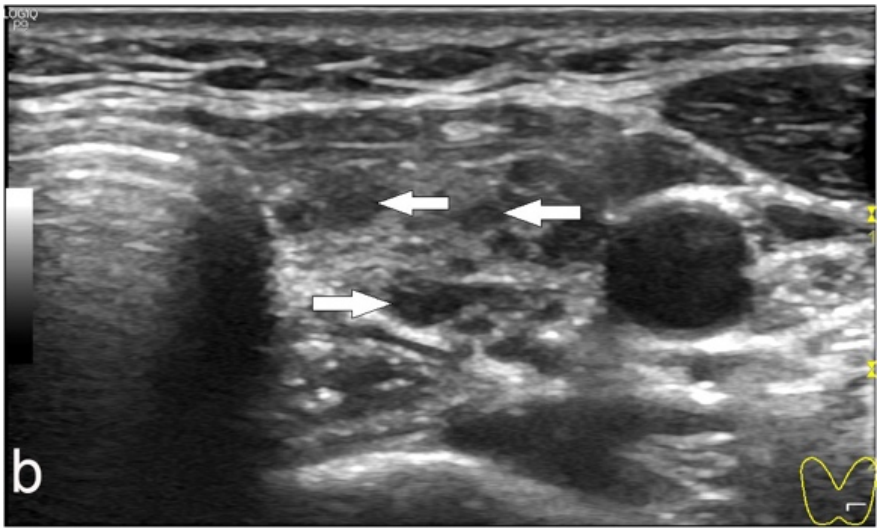
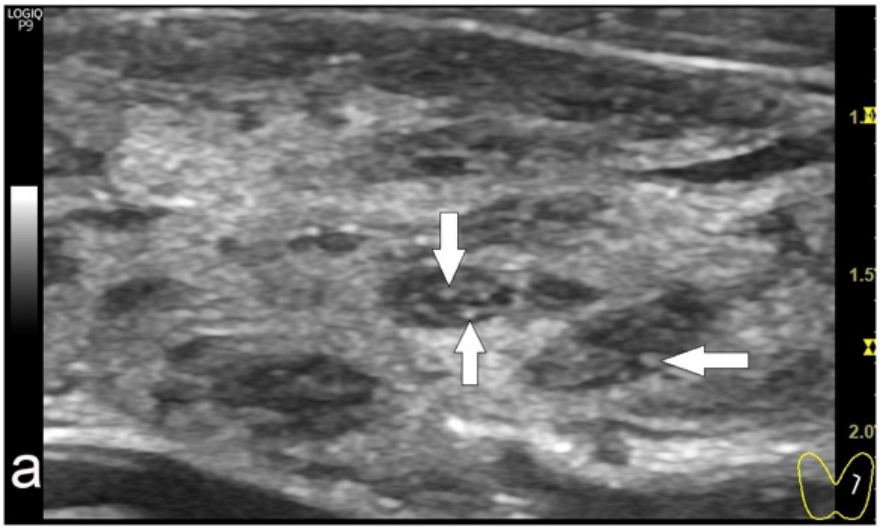


Figure 2. The left lobe of the thyroid gland (**A** is the transverse, and **B** is the longitudinal views) in a 36-year-old female patient (hypothyroidism –TSH up to 10–30 μIU/ml, but replenished with levothyroxine up to euthyroidism; TPOAb 868 [<18.0], TGAb 3.7 IU/ml [<5.6]). Among the isoechoic tissues, small and large lymphoid lobules are identified (arrows). Destruction phase with lymphoid hyperplasia.

After a certain period, a point hyperechoic or isoechoic element, representing an islet of regenerating thyrocytes, might be visible among the hypoechoicity inside such lobules (Figure 3). Gradually, the regeneration zone becomes larger, filling the entire lobule (Figures 4, 5).



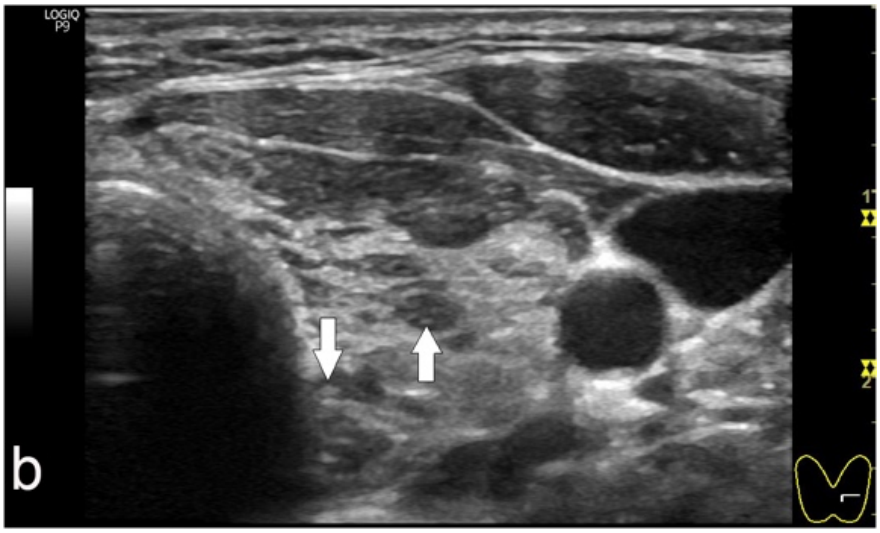
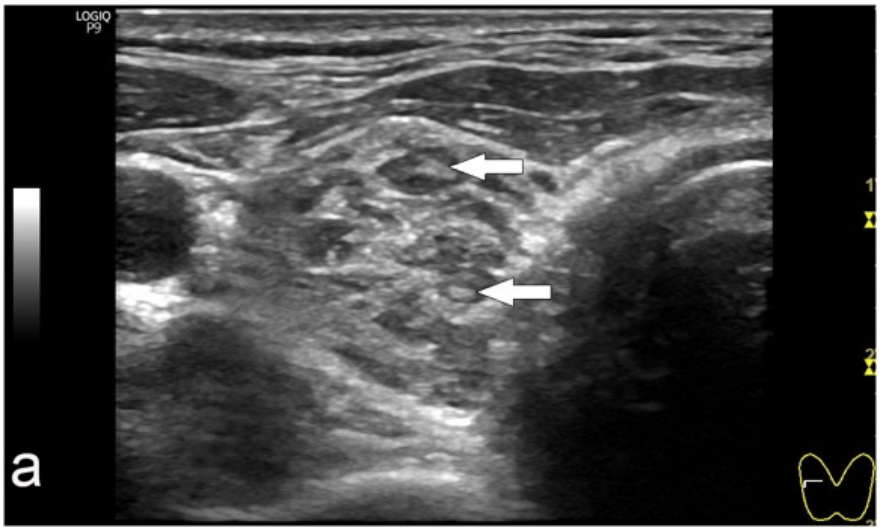


Figure 3. The left lobe of the thyroid gland in a 38-year-old female patient (euthyroidism; TPOAb 700 [<5.6], TGAb 12 [<4.1]). Large lymphoid lobules with hypoechoic tissue are visible, within which several small (point) isoechoic and few hyperechoic inclusions (arrows) representing islets of proliferation of thyroid tissue are seen. It is the initial step of the regeneration phase.



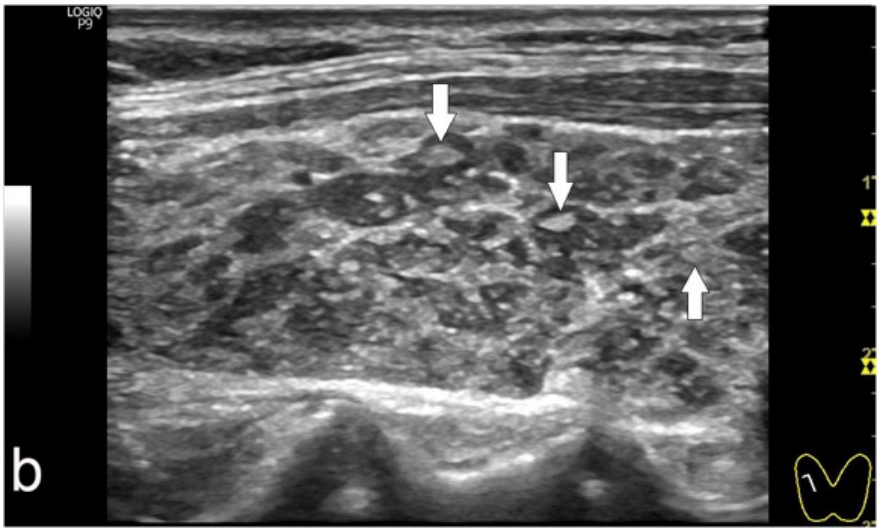
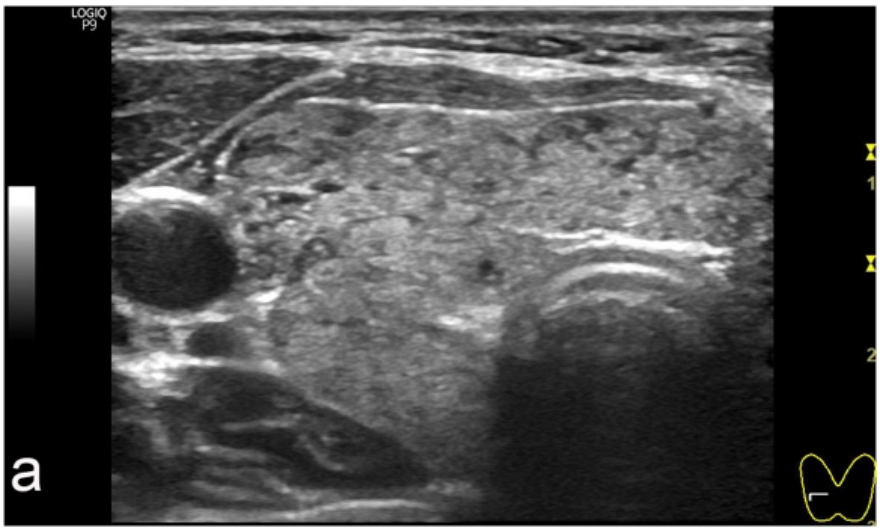


Figure 4. The right lobe of the thyroid gland in a 64-year-old female patient (hypothyroidism –TSH up to 10 μIU/ml, but replenished with levothyroxine up to euthyroidism; TPOAb 1230 [<5.6], TGAb 7 [<4.1]). Large lymphoid lobules with hypoechoic tissue are visible, in the center of which large (arrows) and small isoechoic areas of tissue representing areas of reparative regeneration are detected. It is the active stape of the regeneration phase.



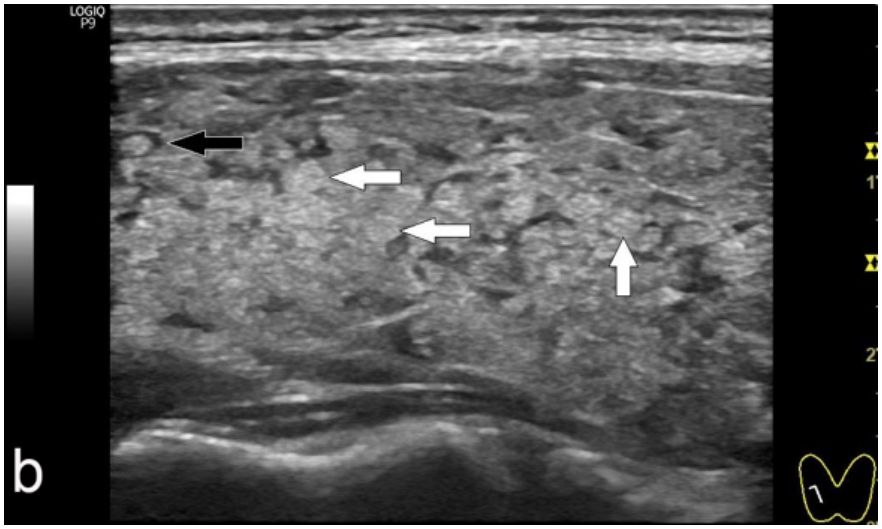
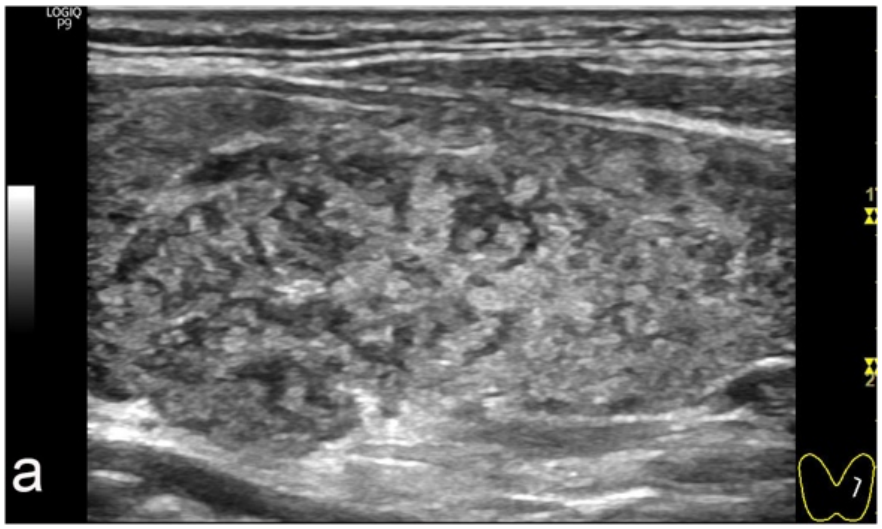


Figure 5. The right lobe of the thyroid gland in a 48-year-old female patient (hypothyroidism: TSH 14.5 IU/ml [0.4–4.0], free triiodtironine (FT3) 3.8 pmol/L [2.6–5.7], free thyroxine (FT4) 9.2 pmol/L [9.0–19.1]; TPOAb >2000.0 [<5.6], TGAb 7.0 [<4.1]); she does not take the hormonal drug. A significant number of spherical isoechoic areas of tissue surrounded by thin and thickened arcual hypoechoic contours are visible (white arrows). It is the final step of the regeneration phase. A small number of lobules in the active step of the regeneration phase are visible (a wider contour of the hypoechoic tissue is detected around the isoechoic tissue area (black arrow)).

All these phenomena correspond to **the general regeneration phase** , consisting of the **initial** , **active** , and**final** steps.

With ultrasound, the final step of the intralobular regeneration phase is characterized by hyperechoic thin sickle-shaped elements representing the remains of the lymphoid tissue along the edge of the lobule (Figure 5). Different phases of the reparative process in the lobules can be simultaneously present in the thyroid gland (Figure 6). In this case, one of the phases can prevail (Figures 1, 4, 5).



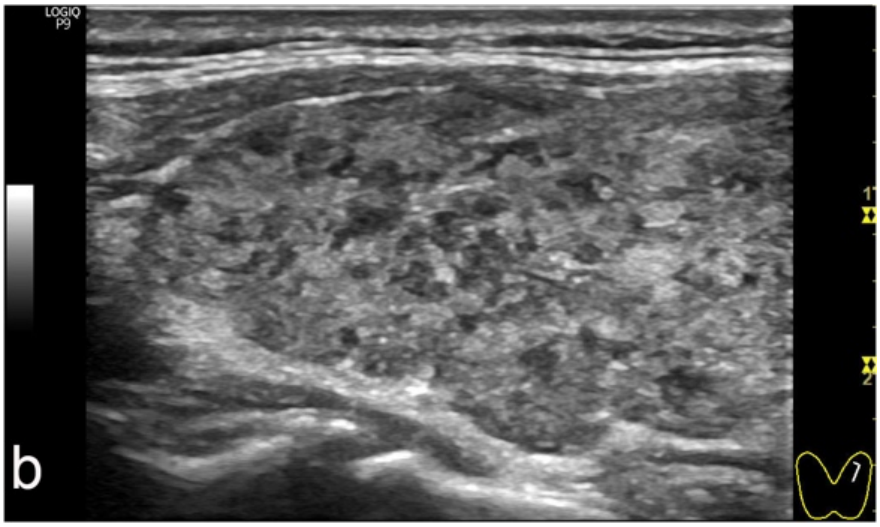


Figure 6. In the left lobe of the thyroid gland in a 56-year-old female patient, regenerative intralobular changes characteristic of different phases (TSH 12.6 μIU/ml [04–4.0], FT3 3.9 pmol/L [2.9–4.9], FT4 9.6 pmol/L [9.0–19.0]; TPOAb >1000 [<5.6], TGAb 49 [<18.0]; she does not take the hormonal drug). **A** is the central part, and **B** is the cranial part of the lobe (longitudinal view).

Intralobular regeneration can end with the normalization of the thyroid gland structure — **the repair phase** . This change occurs with a significant improvement in living conditions and/or rehabilitation treatment for an adequate period.

In case of insufficient substances for the production of hormones and/or unfavorable living conditions (for example, an increase in energy consumption, that is, under the condition of the enhanced need in thyroid hormones known as participating in the basal metabolism and especially in thermogenesis [23]), successive destructive and reparative changes can reoccur in the lobules with the repaired tissue because of overstressing — in accordance with the indicated phases.

The duration of each phase of the lobular process in the thyroid gland also depends on individual circumstances, including those associated with unfavorable living conditions, in which the body increases the stimulation of the thyroid gland, leading to the depletion and destruction of the thyrocytes in the lobules. Therefore, the destruction phase (with different severity of lymphoid proliferation) or the regeneration phase, with the involvement of many lobules and the development of stromal fibrosis of varying severity, can be observed with ultrasound for many years (Figure 7).

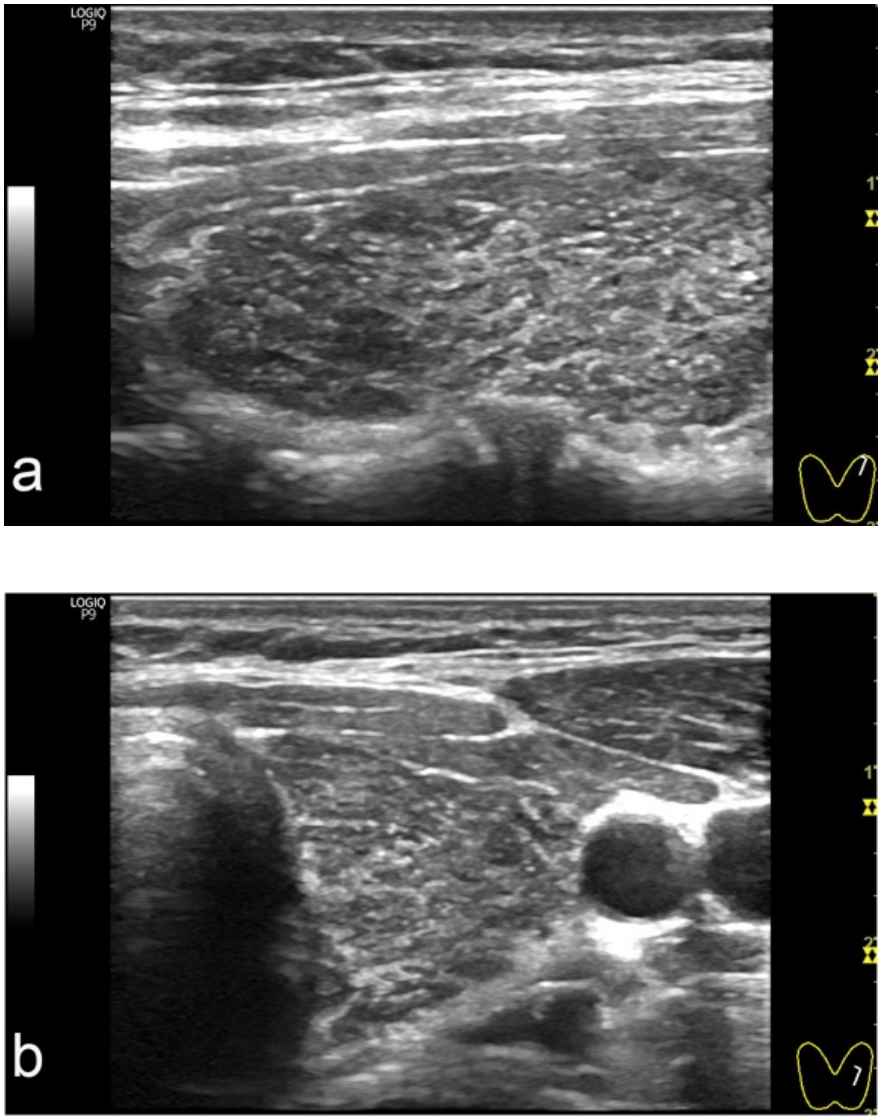


Figure 7. The left lobe of the thyroid gland in a 31-year-old female patient (hypothyroidism – TSH up to 10–30 μIU/ml, but replenished with levothyroxine up to euthyroidism; TPOAb 240 IU/ml [<30], TGAb 20 IU/ml [<30]; she has been taking levothyroxine 100 μg/day for several years). **A.**Longitudinal view of the lobe. **B.** Transverse view of the lobe. In the lobe, a significant number of hypoechoic (lymphoid) lobules were determined, a small part of which was surrounded by hyperechoic tissues (thickening of the connective tissue). Among the hypoechoic tissues, small point isoechoic elements (areas of regeneration) were present in a moderate amount.

In some cases, the intralobular regeneration process can become excessive. A regenerative islet of the isoechoic tissue can grow to a maximum size of 10-20 mm or more, demonstrating itself as a nodule (Figure 8). Bonavita et al., who called it "white knight" [19], reported such nodule regeneration in HT in 2009. Currently, some researchers classify such nodules as benign [24], despite some doubts by the American College of Radiology Thyroid Imaging Reporting & Date System Committee [25].

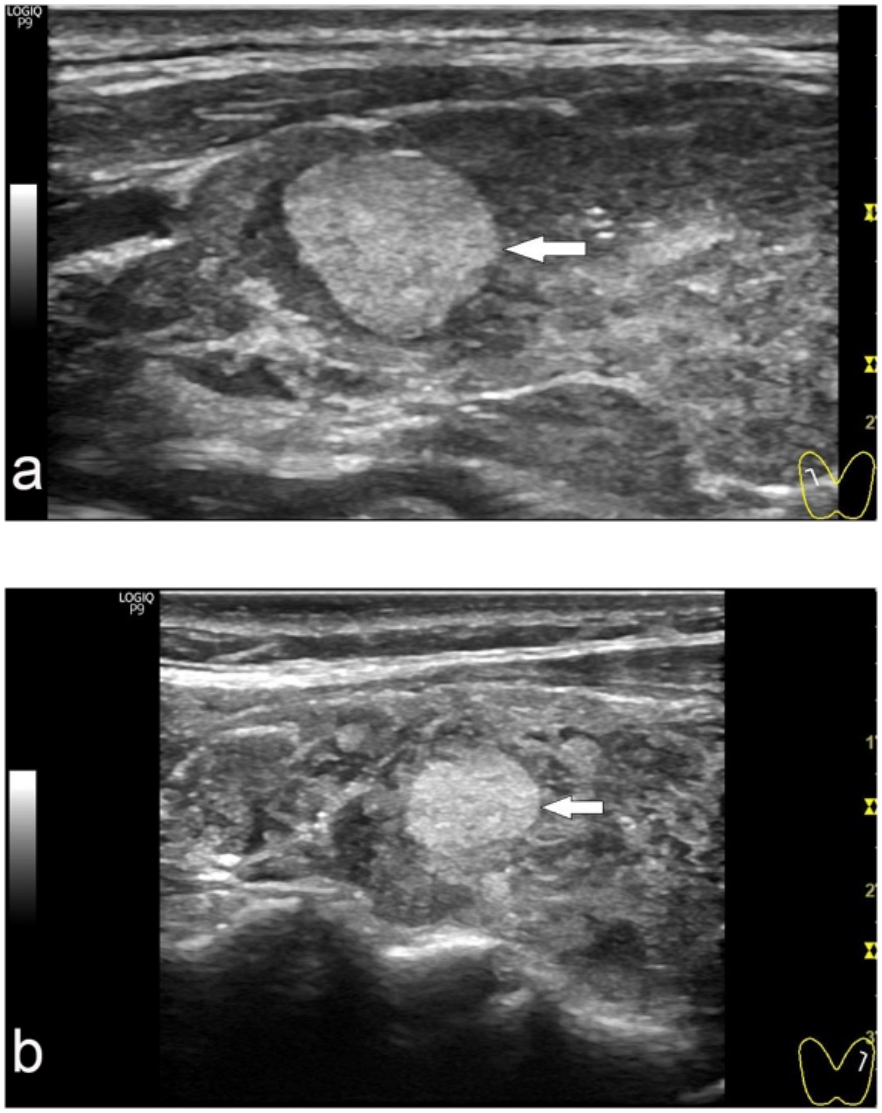


Figure 8. Reparative nodules of the thyroid gland (arrows) or "white knight" by Bonavita et al. [19]. **A.** The reparative nodule of the right lobe of the thyroid gland in a 32-year-old female patient (hypothyroidism – TSH up to 10 μIU/ml, but replenished with levothyroxine up to euthyroidism; TPOAb 659 IU/ml [<100], TGAb 5 IU/ml [<30]). **B.** The reparative nodule of the left lobe of the thyroid gland in a 67-year-old female patient (hypothyroidism – TSH 10.0 IU/ml [0.4–4.0], FT3 3.7 pmol/L [2.6–5.7], FT4 9.3 pmol/L [9.0–19.1]; TPOAb >1000.0 [<5.6], TGAb 8.0 [<4.1]). Small and large isoechoic (regeneration) areas are visible among the hypoechoic (lymphoid) tissues.

Discussion

The regeneration process of the thyroid gland is rarely discussed in the recent guidelines on endocrinology and radiology, despite the real nature and the numerous studies on this phenomenon since the middle of the last century [26, 27]. Sonographic signs of thyroid regeneration have always been found to various extents on ultrasound. However, they were left without appropriate attention. For example, intralobular regeneration is noticeable even in some images in the publication by Yeh et al. [5].

To be fair, I myself noticed the regeneration process inside the lymphoid lobules only a few years ago despite

the fact that I observed general regenerative repair in the thyroid gland with ultrasound much earlier. Perhaps this finding was due to the replacement of my ultrasonograph with a better one.

Regardless of their position as clinicians and sonologists, morphologists and physiologists regularly investigate and confirm the regenerative processes in the thyroid gland. Some of them have analyzed the physiological regeneration of the thyroid gland. For example, Coclet et al. revealed 100% natural renewal of the thyroid tissue *in vivo* without pathology every 8.5 years [28], and according to Dumont et al., the thyroid gland is regeneratively renewed completely every 5 years [29]. Others have identified a significant increase in the rate of reparative regeneration after thyroid surgery [30-34].

Still, others have investigated reparative regeneration with an assessment of hormone metabolism. For example, in an *in vivo*experiment in mice, Chen et al. confirmed intensive restorative regeneration of the thyroid tissue with simultaneous erosion of the lymphoid tissue from the thyroid gland, a decrease in antibodies to thyroglobulin, and normalization of TSH, FT4, and FT3 levels in blood plasma [35]. Other researchers have paid attention to the active regeneration of the thyroid parenchyma in subacute thyroiditis [36,37], especially in comparison with HT [38].

Some have explored the role of stem cells in the regeneration of the thyroid gland, the mechanisms of transition to active proliferation, and the identification of their activity [39, 40 and others]. Some have explored the cultivation of functional thyroid follicles (organelles)*in vitro* for subsequent transplantation as a mini-organ [41].

Such a relatively active interest in thyroid regeneration, its evaluation, and practical implementation is still one-sided. The insufficient attention from clinicians and radiologists to thyroid regeneration could be attributed to the absolutization of the hypothesis of HT and the formal detection of the ultrasound HT pattern — pseudonodules in the thyroid parenchyma — instead of researching the essential features of this process.

All processes in a living body occur in accordance with natural laws. The phenomenon of thyroid regeneration is one such process. Regeneration is usually accompanied by the depletion and destruction of the thyroid tissue and has a different pronouncement. Regeneration of the thyroid gland is a natural process.

The world we live in is constantly changing, and this is a pattern too. New facts and knowledge that appear in our lives influence the scientific worldview and lead to the correction of previous hypotheses. In this case, the process of reparative regeneration represents an important knowledge in improving our understanding of autoimmune processes in the thyroid gland. The possibility of ultrasound control of thyroid regeneration in autoimmune (Hashimoto) thyroiditis is especially important in clinical medicine. This way, the ratio of destructive and reparative events in the thyroid gland could be easily controlled.

Certainly, intelligent systems that allow an accurate assessment of the degree of lymphocytic infiltration and lymphoid lesions separately for each lobe and isthmus while simultaneously identifying the signs of regeneration, its quantitative pronouncement, and proliferation in the gland are required to help radiologists. Such systems will enhance the accuracy of the thyroid ultrasound. Clinical ultrasound diagnosis will replace the formal one based on conventional sonographic patterns.

Conclusion

Knowledge of the compensatory processes in the thyroid gland, which are manifested as reparative regeneration and lymphoid utilization, should orient the specialists toward the real possibility of repairing the thyroid gland structure. Therefore, investigating clinically applicable morphological and physiological patterns of regeneration in thyroid pathology, as detected by ultrasound, is an important and promising concept in endocrinology.

Data availability

The data used to support the findings of this study are included within the article.

Consent

Informed consent was obtained from the patients for their anonymized information to be published in this article.

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Declaration of competing interests

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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