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Chapter 9

The Role of Ultrasound in the Differential Diagnosis of Hypothyroidism

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1. Introduction

Over the last decades, ultrasound has become the leading imaging technique used in the diagnostic workout of thyroid diseases. Thanks to rapid technical improvement, we are now able to differentiate precisely even very small lesions in the thyroid tissue, which previously would have stayed unrecognised. Similarly, the Doppler techniques are able to visualise blood perfusion in the thyroid parenchyma, thyroid nodules and lymphatic nodes with an excellent precision. Due to its availability, low financial cost, noninvasivity and a lacking radiation load, ultrasound is widely used as the imaging method of choice in the diagnosis of thyroid pathologies. In many countries, it has replaced radionuclide techniques, which are now being used only in specific diagnostic questions or in the treatment of selected thyroid disorders.

In this Chapter, we are going to review the role of thyroid ultrasound in the diagnostic workout of thyroid diseases with focus on hypothyroidism. We are going to discuss ultrasound appearance of the thyroid tissue in various thyroid diseases leading to thyroid dysfunction, including thyroid disease in pregnancy and postpartum thyroiditis. We are also going to present interesting cases from our experience.

1.1. Basic principles of ultrasound

As many other important inventions, ultrasound was originally developed for military purposes. It was used in World War I and II in the location of submarines. Sonar was able not only to precisely measure the depth of a reflecting surface under water, but it could also identify an object in motion. In 1950, ultrasound was introduced into medicine as a research

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tool in the USA; and in 1965, the Jutendo Medical Ultrasound Research Centre in Japan was founded [1].

Basically, an ultrasound probe acts as a transmitter and a receiver of ultrasound waves at the same time. Visualisation of a structure of an organ is made possible by an analysis of the received altered ultrasound waves that were reflected and refracted at the interfaces of various tissues. Ultrasound is a longitudinal sound wave of frequency higher than 20 kHz. For medical purposes, the usually used frequency varies between 2-18 MHz, depending on the examined tissue (for thyroid ultrasound typically 7.5-10 MHz). The source of these waves is a quartz crystal placed in a transducer probe. It generates and receives waves using piezoelectric effect, which is based on rapid deformation of a piezoelectric crystal by an applied electrical charge. Accordingly, when the piezoelectric crystal absorbs the mechanical energy of ultrasound waves, it produces an electric current. This ability is used for the detection and display of the reflected waves. The wave reflection occurs at the interface of tissues with different acoustic impedance. The greater the difference in impedance of each tissue, the greater the amount of energy reflected back.

Tissues with frequent interfaces such as normal thyroid gland display as hyperechogenic area; in contrast, structures with no interfaces such as cysts full of liquid are anechogenic. Two-dimensional map of the layout of echogenicity is called B-mode and it is used as the basic display mode in thyroid sonography. Another mode used for displaying the vascularisation of tissue is the Doppler mode. It is based on Doppler's effect: the shift in frequency and wavelength of reflecting waves caused by reflection from moving objects (red blood cells circulating in vessels). This frequency shift displays as a colour-coded overlay on top of a B-mode image (colour Doppler) [2].

1.2. The use of thyroid ultrasound in the world

The indications for thyroid ultrasound (TUS) vary considerably across the world, as well as the availability of ultrasound devices and physicians´ competences. According to the guidelines of the American Thyroid Association (ATA) for management of hypothyroidism, the "uncomplicated hypothyroid patients are usually observed by primary care physicians and there is no recommendation to do TUS in these patients" [3]. In Europe, the situation is different: many hypothyroid patients with Hashimoto thyroiditis are followed by an endocrinologist during their whole life. For example, in our country (the Czech Republic), TUS belongs to the elementary diagnostic methods in the diagnostic process (together with the laboratory assessment of the thyroid stimulating hormone /TSH/, free thyroxine /FT4/and autoantibodies against thyroid autoantigens).

While in the United States the TUS is usually performed by a radiologist and it is used primarily in the management of thyroid nodules and thyroid carcinoma, the European endocrinologists do the ultrasound often themselves in their outpatients departments. In Europe, thyroid ultrasound is used much more frequently than in the USA, e.g. if the cause of hypothyroidism is unclear; in the differential diagnosis of hyperthyroidism, in amiodarone-induced thyroid disease etc. (Kahaly et al. 2011).

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1.3. The ultrasound image of a normal thyroid gland

In order to interpret the ultrasound findings correctly, it is important to be familiar with the anatomy of the thyroid gland. The thyroid is situated in the anterior region of the neck, below the thyroid cartilage with the isthmus located inferior to the cricoid cartilage. In the transversal plane, thyroid lobes are bounded by infrahyoid muscles (anteriorly), trachea (medially), carotid arteries (laterally) and oesophagus (usually on the left) and prevertebral fascia (posteriorly) (Fig. 1). In the elderly, the thyroid gland shifts caudally and often partially retrosternally. In general, the right thyroid lobe is larger than the left one. Rarely, we may visualise the processus pyramidalis as a thin finger-like structure emerging from the isthmus. It is important to check the presence of absence of the lobus pyramidalis especially in patients planned for total thyroidectomy – we have encountered a relapse of Graves´ disease in a forgotten lobus pyramidalis after total thyroidectomy. Anteriorly, the lobes are covered by the infrahyoid and laterally by the sternocleidomastoid muscles. These muscles are important for the evaluation of the echogenicity of the thyroid parenchyma: a healthy thyroid is relatively hyperechogenic as compared to the echogenicity of the muscles.

The size of the thyroid is calculated in millilitres as the sum of the volumes of both lobes (isthmus is neglected). The volume of one thyroid lobe is calculated as:

V (ml) = width x depth x length x 0.479 (cm)

Normal thyroid volume in females is less than 18 ml and in males less than 22 ml. In our experience – in an iodine-sufficient country – the thyroid volumes are generally much smaller (irrespective of the thyroid function) [4]; and true goitres are rare. The lower threshold of normal thyroid volume has not been determined.

The blood is supplied to the thyroid abundantly by the superior and inferior thyroid arteries. Thyroid veins form a thick plexus around the gland. Sometimes, relatively strong vessels occur also inside the parenchyma and it is important to differentiate them from pseudocysts or small hypoechogenic nodules by the Doppler or by the movement of the probe. Perfusion of the thyroid increases on several occasions: in the settings of an increased cardiac output (a stressed patient), in gravidity, during an active autoimmune inflammation – active Graves´ disease or Hashimoto´s thyroiditis and in untreated primary hypothyroidism because of TSH stimulation. In Graves´ disease, the perfusion is very high (typically of the image of a so called "thyroid inferno"). Doppler imaging of the thyroid perfusion is crucial in the differential diagnosis of thyrotoxicosis: increased in Graves´ disease and hyperfunctioning nodules, decreased in breakdown of the thyroid tissue – as is the case of postpartum thyroiditis, De Quervain thyroiditis or amiodarone-induced thyrotoxicosis type 2.

2. The use of TUS in the differential diagnosis of hypothyroidism

Thyroid ultrasound is crucial in the differential diagnosis of hypothyroidism, particularly, if thyroid antibodies are negative. It allows us to determine whether the thyroid is present and

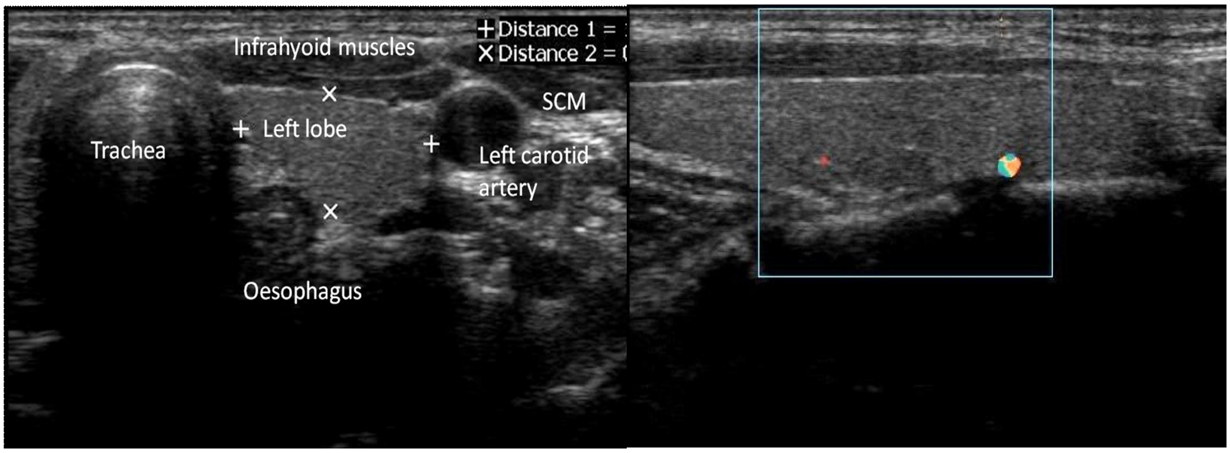

Figure 1. Normal TUS image of left thyroid lobe (euthyroid patient with negative thyroid autoantibodies). Note the low perfusion on the Doppler imaging (right).

to visualise the parenchyma. In this part of the Chapter, we will summarise the ultrasound findings in individual causes of hypothyroidism.

2.1. Rare causes of hypothyroidism

Inborn developmental defects belong among the very rare causes of hypothyroidism: most often hypoplasia, less frequently agenesis or hemiagenesis of the thyroid gland; and ectopic thyroid tissue. These defects are generally diagnosed in early childhood. In children, TUS is performed in cases of positive screening for congenital hypothyroidism. Moreover, scintigraphy may provide the best information on developmental thyroid defects.

2.2. Postoperative states

Hypothyroidism may also develop in patients after total thyroidectomy without an adequate levothyroxine substitution. TUS is important especially in elderly patients with a cognitive deficit and without an obvious scar on the neck. Moreover, TUS should be performed in all patients after total thyroidectomy in order to evaluate a possible presence of a residual thyroid tissue. After thyroidectomy, TUS shouldn´t be performed earlier than two or three months after operations due to the tissue oedema. Patients with thyroid residue should be substituted with higher doses of levothyroxine in order to achieve serum TSH levels in the lower part of the normal reference range (due to an increased risk of thyroid carcinoma in remnant thyroid tissue). Ultrasound image of a patient after total thyroidectomy is shown in Fig. 2.

2.3. Iodine deficiency

From the global point of view, iodine deficiency constitutes a major epidemiological problem. According to the WHO statistics, approximately 13% of the world population has a goitre caused by iodine deficiency [5]. In the developed countries, severe iodine deficiency contributes to the manifest hypothyroidism only to a small extent, although even a milder deficiency may predispose to thyroid dysfunction, e.g. in pregnancy. The typical ultrasound finding in

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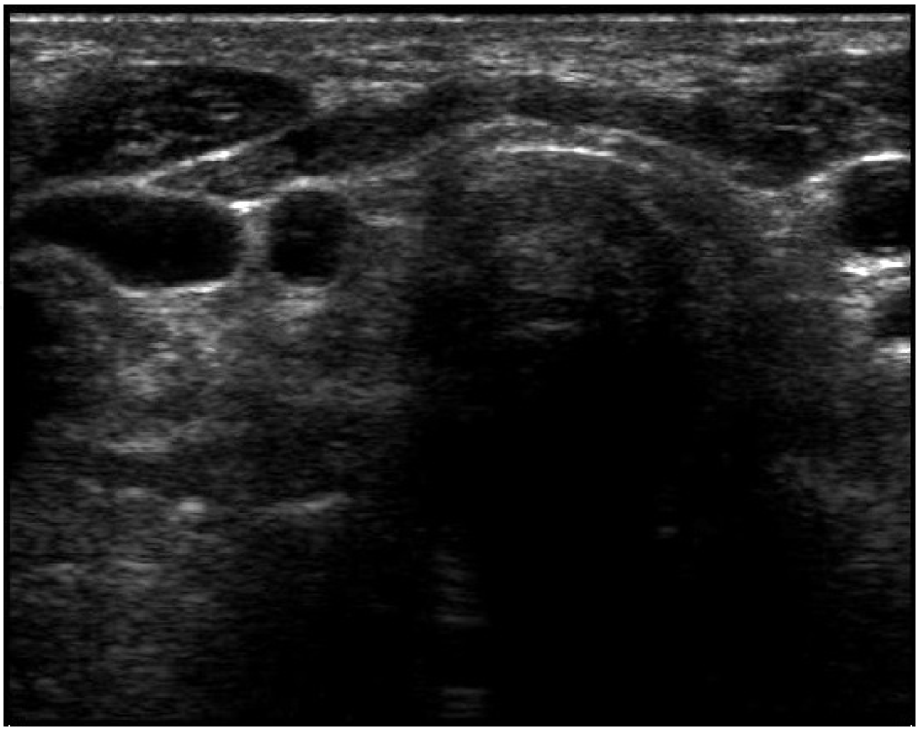

Figure 2. Absent thyroid gland in a patient after total thyroidectomy due to papillary thyroid carcinoma. Note fibrous tissue without residual thyroid parenchyma in the thyroid beds.

iodine deficient patients is a diffuse goitre which often becomes nodular (Fig.3). The perfusion is normal. Enlargement of the thyroid gland is an adaptive process in low iodine intake and it can sometimes lead to dysphagia or dyspnoe due the compression of oesophagus and trachea, respectively. Narrowing of the trachea may be visualised on TUS, but the goitre often reaches below the sternum and it is thus inaccessible for TUS examination. In these cases, we indicate CT scan in order to describe the size of the gland and the extent of trachea compression. Such information are crucial for the decision whether to operate and from which surgical access (classical or through sternotomy).

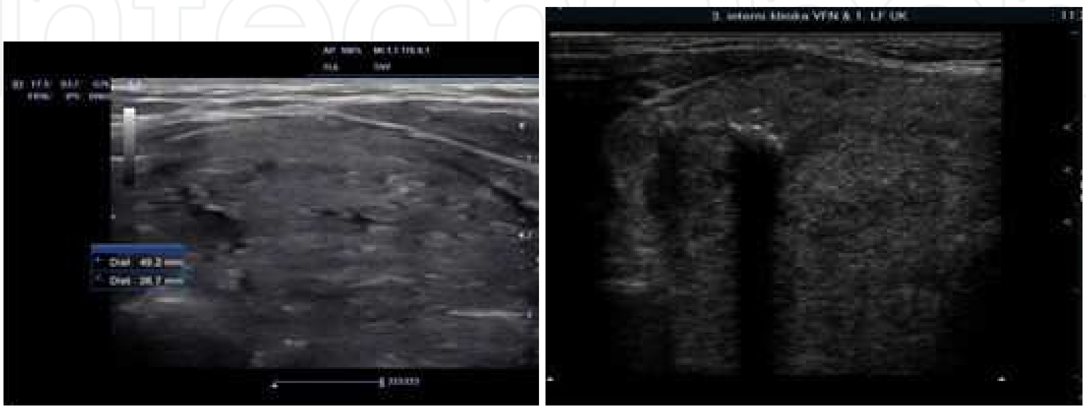

Figure 3. TUS of a diffuse goitre in a euthyroid patient (on the left) and multinodular goitre (on the right).

2.4. Hashimoto´s thyroiditis (autoimmune thyroiditis)

The most common cause of hypothyroidism in iodine sufficient areas is the Hashimoto´s thyroiditis - HT (autoimmune thyroiditis, chronic lymphocytic thyroiditis). HT with the presence of goitre may be more frequently observed in iodine-deficient areas, whereas the majority of patients with HT in iodine- sufficient areas have a normal thyroid volume. In Greek children, the thyroid volume was associated with the degree of hypothyroidism, it positively correlated with serum TSH concentrations, and it decreased after treatment with levothyroxine [6], [7]. The typical TUS appearance of autoimmune (Hashimoto´s) thyroiditis includes an inhomogenous, hypoechogenic pattern (as compared to the echogenicity of the neck muscles). Vascularisation of the thyroid gland may be diffusely increased (Fig. 4). In cases with severe hypothyroidism with TSH up to 100 mIU/l and more, which may occur e.g. after delivery, the thyroid gland increases dramatically its volume and the ultrasound image may be one of a very hypoechogenic goitre with fibrotic septae (honeycomb-like) (Fig. 5).

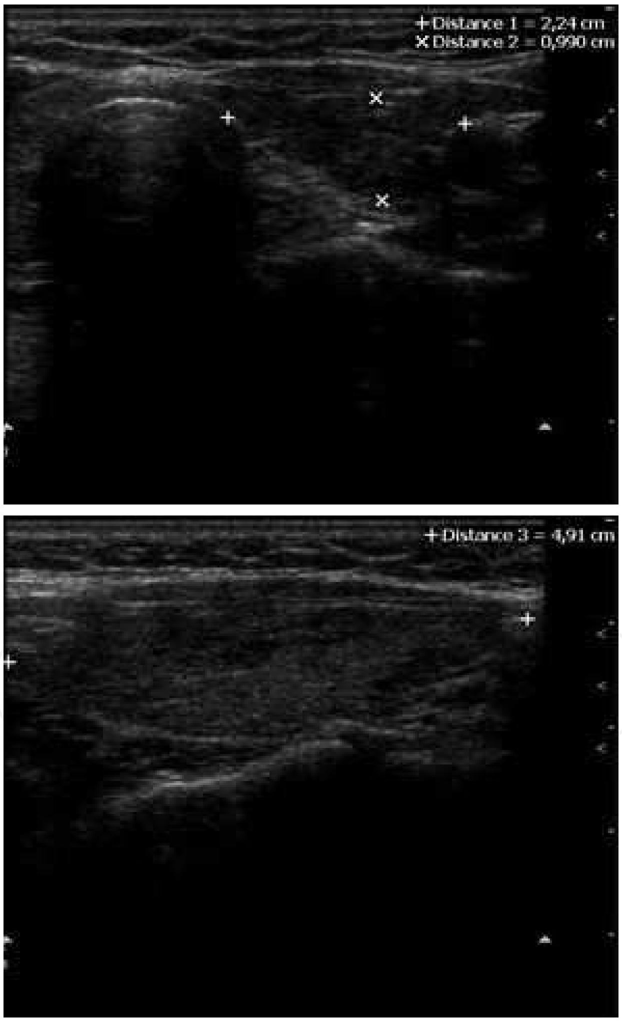

Figure 4. Typical TUS image of Hashimoto´s thyroiditis (TSH 17 mIU/l, highly positive thyroid autoantibodies). Note the inhomogenous and hypoechogenic thyroid texture.

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Figure 5. TUS image of the right thyroid lobe in a patient with Hashimoto´s thyroiditis with a large goitre.

It is important to mention that Hashimoto´s thyroiditis may also have a different appearance on the ultrasound. Atrophic thyroiditis is a common variant of HT, especially in a long-term active disease. A progressive fibrotisation in the inflammatorily changed tissue may lead to an atrophy of the parenchyma with a significant reduction in the thyroid volume. This corresponds to the ultrasound finding of a very small and inhomogeneous thyroid gland, which may be both hypo- and hyperechogenic (in case of an advanced fibrotisation) (Fig. 6).

Moreover, some patients with positive antithyroid antibodies and thyroid dysfunction may have a normal echogenicity of the parenchyma, which is filled with small sharply circumscribed hypoechogenic lesions, which look like moth-eaten (Fig. 7). It is unknown what mechanism predisposes individual patients to which ultrasound image of thyroiditis.

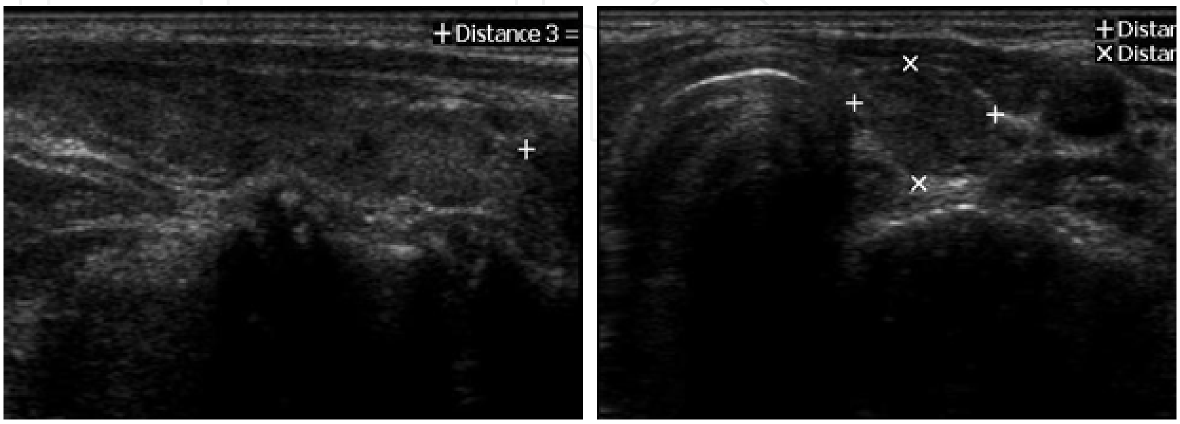

Figure 6. TUS of atrophic thyroiditis (a patient with mild hypothyroidism: TSH 9.43 mIU/l, highly positive anti-TPO antibodies).

Figure 7. TUS picture of a “moth-eaten thyroid” in patient with HT.

TUS does not always correspond to the laboratory results. As we discuss later, the discrepancy between TUS image and the degree of antithyroid antibodies-positivity may be particularly striking during pregnancy.

Usually, upon the diagnosis of hypothyroidism, a positivity of thyroid antibodies is regarded as an evidence of an autoimmune thyroid disease. However, according to some studies, autoimmune pattern in TUS is more specific for the diagnosis of autoimmune thyroid disease (AITD) than the positivity of antibodies. In the study of Rago et al., during three years of follow-up none of the TPOAb-positive patients with negative TUS developed hypothyroidism, in contrast to 58 % of the TPOAb-positive euthyroid patients with positive TUS who became hypothyroid[8]. Moreover, thyroid dysfunction was found in 13.7% of patients with thyroid hypoechogenicity with negative antibodies in comparison to none of the antibody-negative subjects with normal TUS [8]. This suggests that TUS is a useful diagnostic method in the evaluation of the risk of developing hypothyroidism.

2.5. Subacute (De Quervein’s) thyroiditis

Subacute (De Quervein’s) thyroiditis is an inflammatory disease of the thyroid gland, which usually occurs after a respiratory (viral, bacterial) infection. The initial phase of the disease is characterised by hyperthyroidism accompanied by local migrating neck pain, increased temperature and constitutional symptoms (myalgias, arthralgias, fatigue), and elevation of serum acute phase proteins (C-reactive protein) and blood-sedimentation rate. Although it is primarily not an autoimmune disease, approximately 15% of cases can transform into Hashimoto´s thyroiditis and develop a permanent hypothyroidism with positive anti-thyroid antibodies[9]. Typical TUS of subacute thyroiditis consists of irregularly shaped hypoecho-

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genic areas (Fig. 8) which may contrast with areas of normal thyroid parenchyma in the in initial phase. Hypervascularisation is not present. The extent of hypoechogenic areas within the thyroid tissue is a positive predictor of subsequent long-term hypothyroidism – patients with bilateral hypoechogenic areas at presentation had a six times higher risk of developing permanent hypothyroidism than patients with unilateral hypoechogenic areas[10].

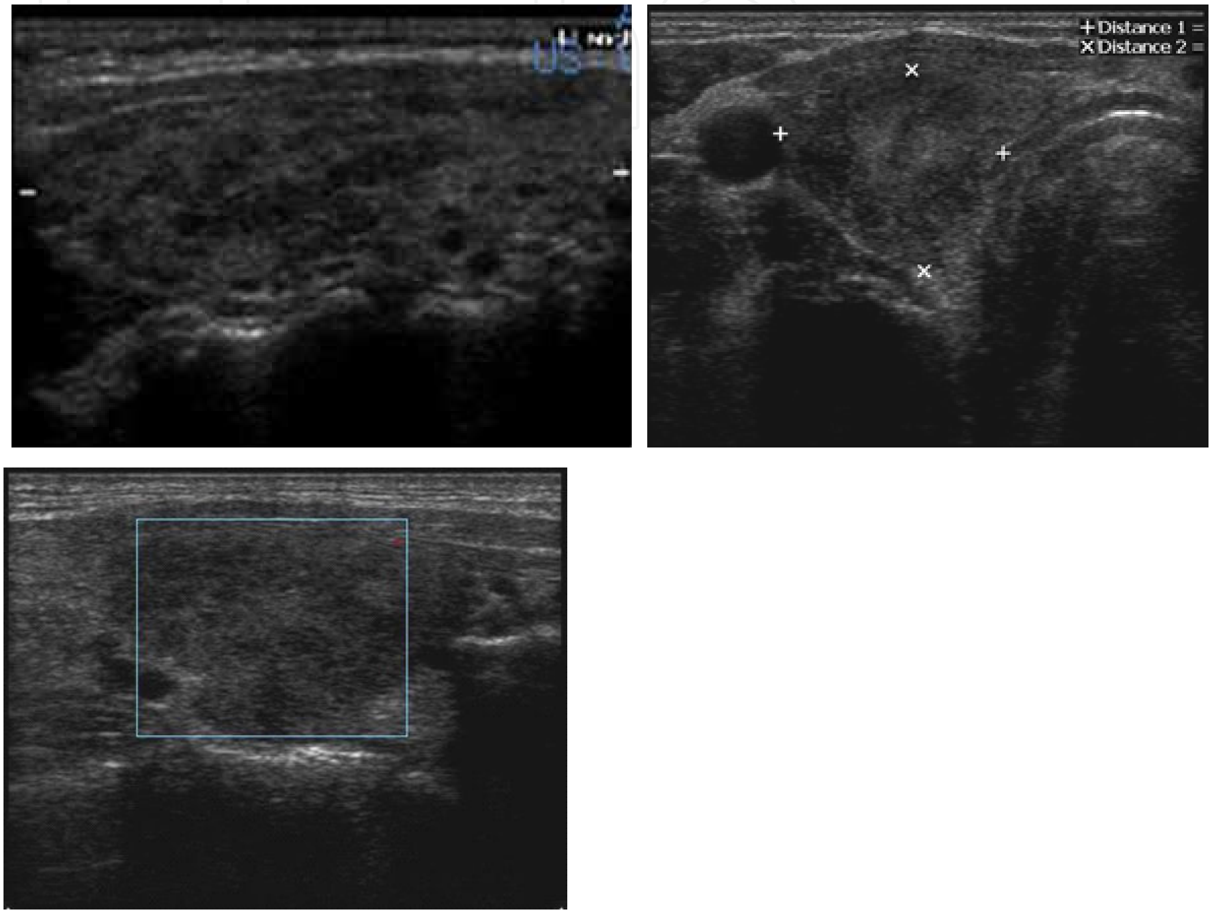

Figure 8. TUS image of subacute thyroiditis in the hyperthyroid phase (FT3: 10.7 pmol/l, FT4: 33.1 pmol/l, TSH: 0.039 mIU/l, antibodies negative). Note the low perfusion as shown by the Doppler imaging (right).

2.6. Amiodarone-induced hypothyroidism

Amiodarone is an antiarrhythmic drug often used in treatment of ventricular and supraventricular tachyarrhythmias. Each tablet contains about 37% (i.e. 75 mg) of organic iodide; 8-17% of which is released as free iodide. Thus, a 100-mg tablet contains an amount of iodine that is 250-times higher than the recommended daily iodine requirement [11].

Autoimmune thyroid dysfunction occurs in up to 22% patients treated with amiodarone, depending on the iodine saturation in the geographical area [12]. Amiodarone can cause both hyper- and hypofunction of the thyroid gland, which may develop both in a normal thyroid gland or in settings of a preexisting thyroid disease. Excessive iodine intake inhibits the synthesis of thyroid hormones in patients with Hashimoto´s thyroiditis and it may worsen the hypothyroidism. High doses of iodine can damage the thyroid follicles and they may accelerate the natural trend of Hashimoto´s thyroiditis toward hypothyroidism [13]. The ultrasound image of amiodarone-induced hypothyroidism may be similar to the typical findings in an autoimmune inflammatory thyroid process – an inhomogeneous hypoechogenic pattern (Fig. 9) ; or the thyroid gland may even have a normal texture.

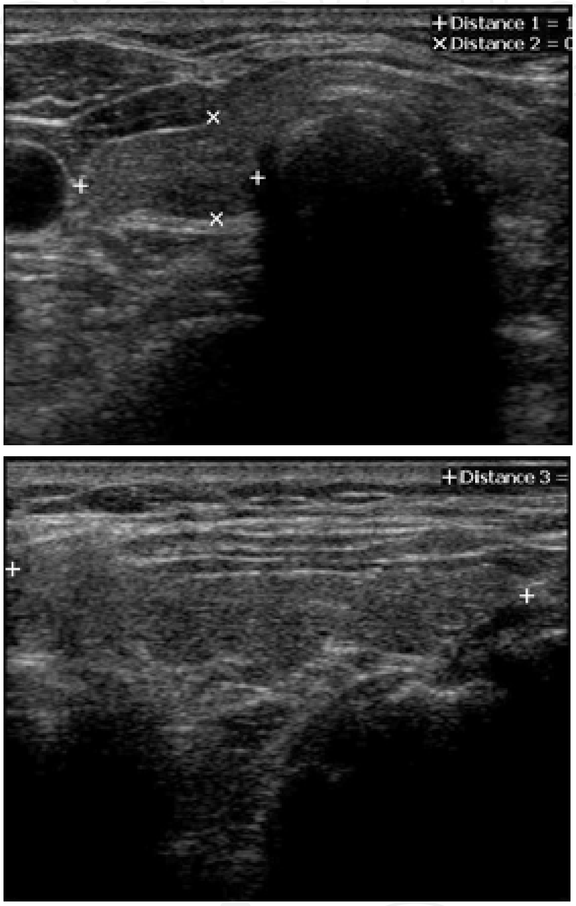

Figure 9. TUS image in a 69-year-old patient who developed hypothyroidism after treatment by amiodarone.

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3. TUS during pregnancy and postpartum

3.1. Changes of TUS image in pregnancy

The relationship between antithyroid antibodies-positivity and the TUS image may change in the settings of altered hormonal state, e.g. in pregnancy. According to our findings, nearly a half (42.5%) of the TPOAb-positive pregnant women do not have an autoimmune pattern in thyroid ultrasound, while in the non-pregnant controls, it was only 22.4% [14]. In our study, we have also shown that the occurrence of hypothyroidism in pregnancy and the rate of preterm delivery

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were linked to an autoimmune pattern in TUS. Thus, a normal TUS image in a TPOAb-positive euthyroid pregnant woman might be a favourable predictive parameter[14].

3.2. Postpartum thyroiditis

The incidence of PPT is reported between 5-10% [15]. Postpartum thyroiditis (PPT) is a disease that occurs in the relationship to pregnancy and it manifests itself by a transient thyrotoxicosis with a following hypothyroidism. Usually, it occurs 2-6 months after delivery and it presents with a few (4-8) weeks lasting hyperthyroidism, which may spontaneously resolve to a euthyroid state or switch to hypothyroidism. Approximately one half of patients do not develop temporary hyperthyroidism and the disease manifests itself by postpartum hypothyroidism [15]. Persistent hypothyroidism develops in 50 % of women with PPT[16]. Moreover, TPOAb-positivity in the first trimester of pregnancy is associated with a higher risk of developing PPT: almost 60% of TPOAb-positive women develop PPT [17], [18].

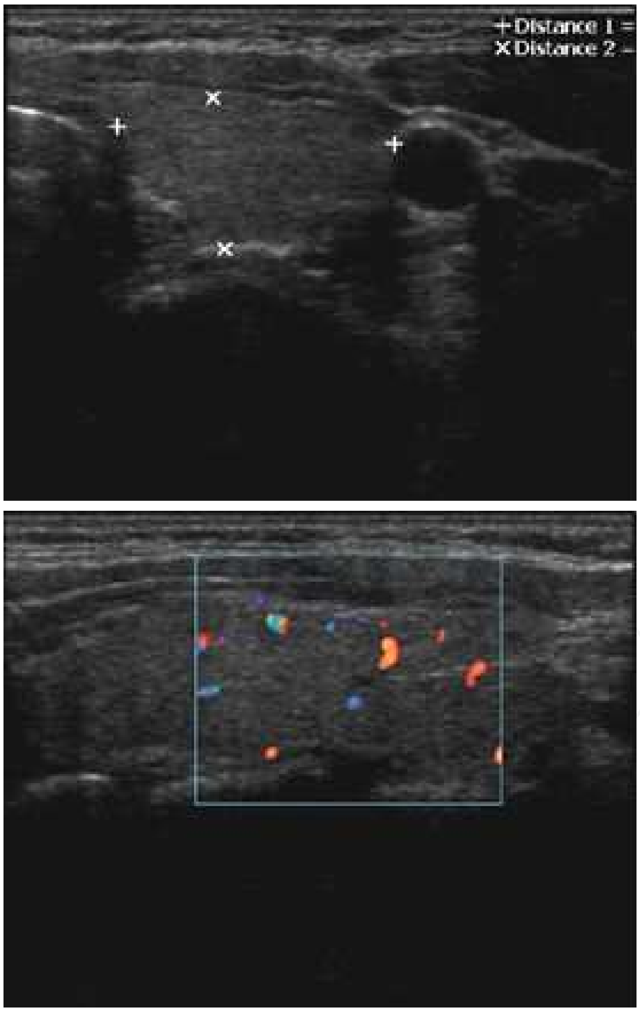

Figure 10. TUS of the left thyroid lobe of patient with PPT which occurred two months after delivery (TSH 0.024 mIU/l, fT4 28.9 pmol/l, TPOAb 746 kIU/l). Four months after delivery, the patient developed hypothyroidism.

The TUS image in PPT in both hyper- and hypothyroid phases includes typical autoimmune pattern (enlargement, inhomogeneous hypoechogenic parenchyma with an increased vascularisation) (Fig. 10). There are no significant differences in the TUS image between these two phases; probably because the transient hyperthyroidism is caused by disintegration of follicles during the inflammation processes in thyroid gland. Higher levels of TPOAb in pregnancy are associated with a higher prevalence of ultrasound changes [19].

4. Interesting cases from our experience

4.1. Healthy women with autoimmune pattern in TUS

A 35-year-old healthy woman with no clinical signs and symptoms of hypothyroidism and a negative history of thyroid disease was examined as a member of a control group in a clinical study. Her thyroid laboratory tests were all normal (Table 1). Surprisingly, the ultrasound examination revealed a typical image of Hashimoto´s thyroiditis: the thyroid parenchyma was inhomogenous and hypoechogenic with an increased vascularisation. After three months, her TUS findings remained unchanged and her TSH was again in the normal range. Next control is scheduled in six months – these results are not yet available at the time of publication of this Chapter.

	First visit	After 3 months	Normal Ranges
TSH (mIU/l)	0.800	1.967	0.5 – 4.9
free T3 (pmol/l)	5.1	-	3.4 – 6.3
free T4 (pmol/l)	14.6	-	11.5 – 22.7
TPOAb (kU/l)	45	-	0 – 60
TgAb (kU/l)	52.5	-	0 – 60

Table 1. Laboratory findings in a healthy woman with a typical autoimmune pattern on thyroid ultrasound (Fig. 11).

It remains unclear whether thyroid dysfunction and/or antithyroid antibodies-positivity will develop at a later stage or whether it is a variant of HT with negative antithyroid antibodies and without progression to hypothyroidism. According to the results of an Italian prospective study, euthyroid patients with autoimmune pattern in TUS are in a significantly higher risk of developing hypothyroidism than those with positive antibodies but normal TUS. Correspondingly, individuals with both positive TUS and antibodies are in a higher risk than those with positive antibodies but normal TUS[8]. It remains unclear how often and how long these patients should be followed.

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Figure 11. TUS image in a young euthyroid woman with negative antithyroid antibodies.

4.2. Thyroid carcinoma in a pregnant woman

A 33-year-old pregnant woman was referred to our Outpatient department due to a small nodule in the right lobe of her thyroid gland. Her laboratory findings were normal (TSH 1.606 mIU/l, FT4: 11.7 pmol/l, negative antibodies). In the third trimester of pregnancy, TUS and fine needle aspiration biopsy (FNAB) were performed. On the TUS, two nodules (one hypoechogenic and one isoechogenic) in the right lobe were visible. The rest of the thyroid tissue had a normal ultrasound pattern. FNAB of the hypoechogenic one (Fig. 12) yielded a diagnostic conclusion of Bethesda V (suspicion of malignancy).

A suppression therapy with 100 ug of levothyroxine per day was initiated. One month after the delivery patient underwent total thyroidectomy with a histological finding of thyroid papillary carcinoma. The tumour was clinically and histopathologically evaluated as low-risk, thus radioiodine ablation was not performed. During one year of follow-up, no thyroid tissue was found on the neck sonography and serum thyroglobulin remained undetectable.

Figure 12. TUS image of a thyroid papillary carcinoma (8x6x12 mm) in a pregnant euthyroid TPOAb-negative woman.

4.3. Hypothyroid patient with AL amyloidosis

A 32-year-old woman with AL amyloidosis affecting the kidneys, liver, spleen, bone marrow and intestine was referred to our Outpatient department in order to evaluate her TSH elevation. The diagnosis of AL amyloidosis was made in 2006 through a kidney biopsy, which was indicated because of a renal insufficiency (creatinine 180 umol/l) and proteinuria (15 g/24h). The affection of other organs was subsequently confirmed by biopsies. At presentation, the patient´s TSH was 8.073 mIU/l, fT4 16.7 pmol/l and antithyroid antibodies were negative. The TUS yielded an image of a mildly inhomogeneous and hypoechogenic thyroid gland with a normal vascularisation (Fig. 13). Cytological specimen obtained by FNAB proved an infiltration of the thyroid tissue by amyloid. It confirmed thus the diagnosis of thyroid amyloidosis. Substitution therapy with 50 ug of levothyroxine was started and the patient is now euthyroid.

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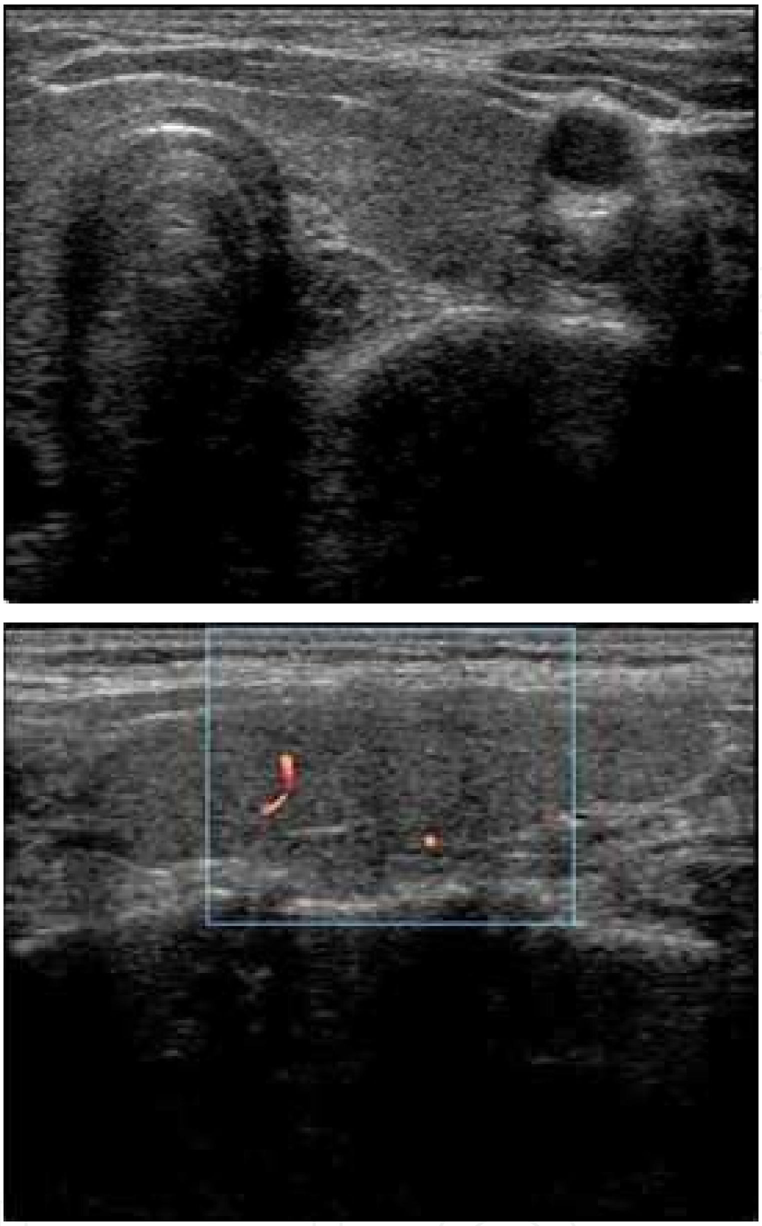

Figure 13. TUS image of thyroid amyloidosis confirmed by cytology.

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5. Conclusion

Thyroid ultrasound is an optimal initial imaging method in the evaluation of thyroid disorders thanks to its noninvasivity, availability and no radiation load. It is widely used not only in the management of thyroid nodules, but also in the diagnostic workup of thyroid dysfunction. In a hypothyroid patient, the TUS may lead to cost savings: if a typical autoimmune pattern is present on TUS, the measurement of antithyroid antibodies is not necessary for the diagnosis of Hashimoto´s thyroiditis. Moreover, the ultrasound image contributes to the decision process whether to treat patients with positive antithyroid antibodies who are euthyroid or have only a mild subclinical hypothyroidism. TUS in this setting is especially valuable in case of women who wish to conceive or are pregnant.

In our opinion, TUS should be performed in all patients with thyroid dysfunction and, in case of young women and pregnant women, also in those who are euthyroid but are positive for antithyroid antibodies. Moreover, we believe that if we, the treating endocrinologists, perform TUS by ourselves, we may improve the care of our patients.

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