Painless thyroiditis associated to thyroid carcinoma: role of initial ultrasonography evaluation

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ABSTRACT

Even though it is a rare event, most associations of thyroid carcinoma with subacute thyroiditis described in the literature are related to its granulomatous form (Quervain's thyroiditis). We present a patient with subacute lymphocytic thyroiditis (painless thyroiditis) and papillary thyroid cancer that was first suspected in an initial ultrasound evaluation. A 30-year old female patient who was referred to the emergency room due to hyperthyroidism symptoms was diagnosed with painless thyroiditis established by physical examination and laboratory findings. With the presence of a palpable painless thyroid nodule an ultrasound was prescribed and the images revealed a suspicious thyroid nodule, microcalcification focus in the heterogeneous thyroid parenquima and cervical lymphadenopathy. Fine needle aspiration biopsy was taken from this nodule; cytology was assessed for compatibility with papillary thyroid carcinoma. Postsurgical pathology evaluation showed a multicentric papillary carcinoma and lymphocytic infiltration. Subacute thyroiditis, regardless of type, may produce transitory ultrasound changes that obscure the coexistence of papillary carcinoma. Due to this, initial thyroid ultrasound evaluation should be delayed until clinical recovery. We recommended a thyroid ultrasound exam for initial evaluation of painless thyroiditis, particularly in patients with palpable thyroid nodule. Further cytological examination is recommended in cases presenting with suspect thyroid nodule and/or non-nodular hypoechoic (> 1 cm) or heterogeneous areas with microcalcification focus. Arch Endocrinol Metab. 2016;60(2):178-82

INTRODUCTION

Destructive thyroiditis is characterized by thyroid inflammation, consequent deregulated release of thyroid hormones secondary to the destruction of the thyroid follicles, and by proteolysis of the stored thyroglobulin (1). Thyroiditis can manifest as neck pain (acute and subacute thyroiditis) or be "silent" (painless thyroiditis). The clinical manifestations of thyrotoxicosis are usually mild, compared with other causes of hyperthyroidism, and it is self-limiting (lasting two to six weeks) (2). Therefore, treatment with beta-blockers is recommended only for symptomatic patients (3). Antithyroid drugs, which inhibit the production of new T_4 are not indicated in the management of patients with hyperthyroidism because symptoms are caused by the release of preformed T_3 and T_4 from the damaged gland (4).

The diagnosis of subacute thyroiditis (SAT) is based on clinical symptoms of hyperthyroidism, suppressed thyrotropin, elevated rate of erythrocyte sedimentation, and/or reduced or absent radionuclide uptake (5). In painless thyroiditis (PT) radioiodine uptake is low; therefore, it is different from Graves' disease as well as from SAT, where patients experience no pain and there is no viral prodrome.

Thyroid ultrasound (US) is not routinely indicated for the assessment of hyperthyroidism and it is usually limited to cases when a nodule is discovered by palpation (6). Characteristic ultrasound features of SAT, especially granulomatous form, are enlargement of thyroid gland, focal hypoechoic zones with indefinite borders or diffuse hypoechoecogenicity, and lack or low flow on color Doppler in these areas (7). Though these ultrasound findings are not pathognomic for SAT and the ultrasound appearances may overlap with other types of thyroiditis and some types of thyroid cancer, but the clinical presentation should allow differentiation. Diffuse hypoechogenicity is also found in Graves' disease and Hashimoto thyroiditis (8), while both benign nodules and thyroid carcinomas can exhibit focal hypoechoic areas (9). In fact, findings in SAT can mimic thyroid carcinoma and marked hypoechoic, ill-defined focal areas may suggest thyroid cancer (10). These ultrasound changes may completely disappear when a re-

mission in SAT takes place (7). Little is known about ultrasound findings of PT and its association with thyroid carcinoma.

Here, we present a patient with subacute lymphocytic thyroiditis (painless thyroiditis) and papillary thyroid cancer first suspected in the ultrasound evaluation during active phase of disease.

CASE REPORT

A 30-year-old woman was being treated at the emergency room because of tachycardia and atypical precordial pain. History revealed that in the previous 2 months she had lost four kg and intermittently experienced sweating and palpitations. There was no history of fever, malaise, neck pain, antecedent upper respiratory infection, drug or iodine exposure nor pregnancy. No family history of thyroid disease. Physical examination showed a regular heart rate of 120 beats/min, a blood pressure of 120/85 mmHg, and axilla temperature of 36.8°C. There was presence of tremors of the extremities. There were no signs of ophthalmopathy or dermopathy. Neck examination revealed a diffusely enlarged and non-tender thyroid gland. Presence of painless nodule in the right lobe of the thyroid gland with a diameter of 2 cm without lymphadenopathy. Her laboratory examinations were as follows: electrocardiogram showed sinus tachycardia, creatine kinase (CK): 38 (26 – 140 U/L), CK-MB: 10 (< 24 U/L), high-sensitivity troponin < 0.02 (0.02-0.06 µg/L), TSH: 0.02 (0.4-4.5 µUI/mL), free T4: 2.8 (0.7-2.0 ng/dL), T3: 230 (70-210 ng/dL), anti-thyroperoxidase: 274 (10-35 UI/mL), erythrocyte sedimentation rate: 5 (0-20 mm/h), C-reactive protein: 3.5 (< 5.0 mg/L), neutrophil: 11690 (3600 - 11000/µL), absolute neutrophil: 6792 (1500-7000/µL), haemoglobin: 14.6 (11.4-16.4 g/dL), and thrombocyte count was 353000 (150000-440000/µL). Radioiodine uptake (^{131}I) was 1% (15-25). Medical therapy was initiated and the symptoms improved with beta-blockers. Thyroid US was carried out using a real time linear array 10-MHz transducer and demonstrated a diffusely enlarged thyroid gland with difuse hypoechoic pattern. There was presence of a 2.0 x 1.8 cm isoechoic nodule on the right lobe and 1.2 x 1.0 cm sized suspicious nodule with irregular border and microcalcifications on left lobe (Figure 1). Microcalcification focus in non-nodular heterogeneous area in right lobe (Figure 2) was described. Suspect lymphadenopathy was found in central neck (Figure 3).

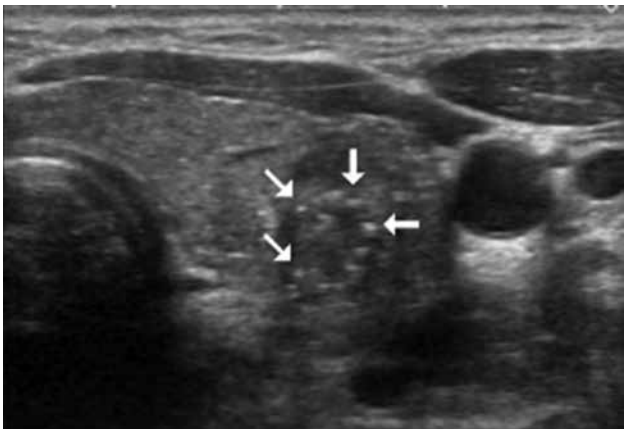

Figure 1. Transversal image of left lobe shows parenquima with heterogeneous changes of lymphocytic thyroiditis and a suspicious nodule with irregular border and microcalcifications (arrows).

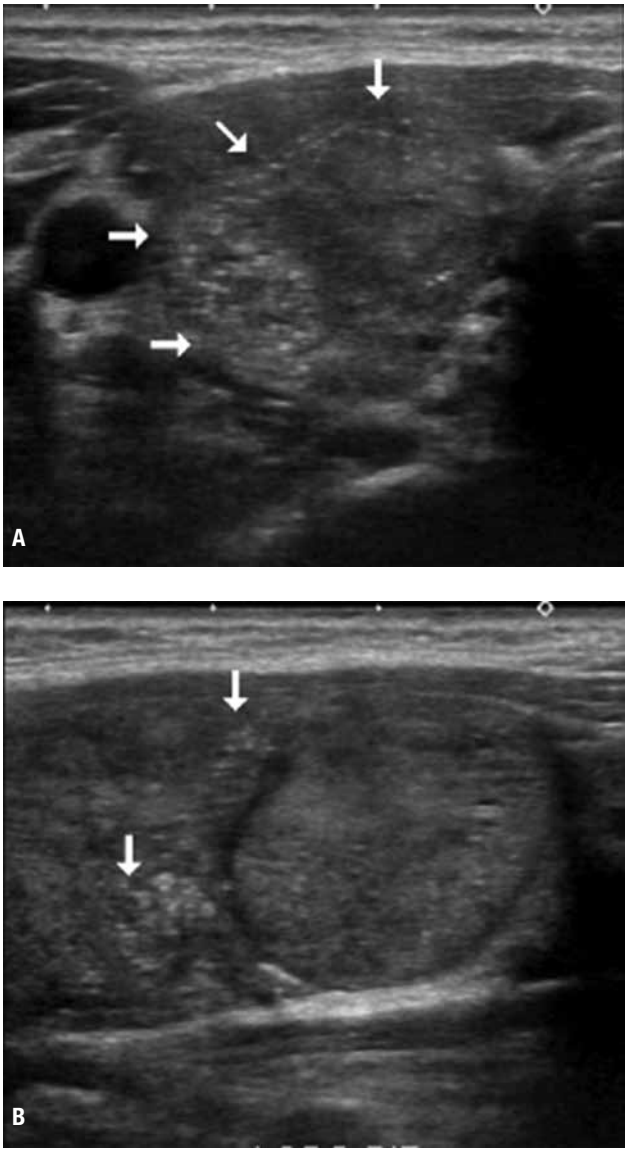

Figure 2. Transversal image of right lobe. (**A** and **B**) Heterogenous areas with microcalcifications in perinodular area (arrows). B. Isoechoic nodular area (not confirmed by histological examination).

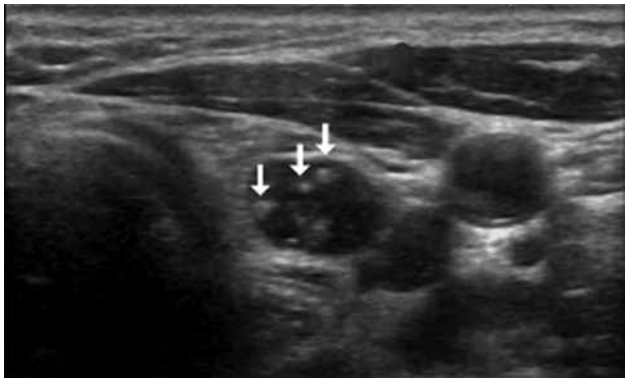

Figure 3. Cervical level VI lymphadenopathy. Presence of enlarged and rounded lymph nodes with microcalcifications (arrows).

The fine needle aspiration biopsy taken from the left nodule and central lymph node revealed a malign cytology and was compatible with papillary thyroid carcinoma. After clinical recovery, a total thyroidectomy and central neck lymph node (level VI) dissection were performed. Postsurgical pathology evaluation was reported to be classical papillary thyroid carcinoma (1.2 cm) on the left lobe and five microcarcinoma lesions (four in right lobe and one in isthmus) from 0.2 cm to 0.8 cm of diameter. There was presence of extensive lymphocytic infiltration (Hashimoto's thyroiditis). Lymph nodes metastasis of papillary thyroid cancer was present.

DISCUSSION

Subacute lymphocytic thyroiditis (painless thyroiditis) is clinically and pathologically similar to postpartum thyroiditis, but it occurs in the absence of pregnancy. It accounts for one percent of all cases of hyperthyroidism. It is considered a variant form of chronic autoimmune thyroiditis, suggesting that it is part of the spectrum of thyroid autoimmune disease (1). Elevated levels of thyroid peroxidase antibodies (anti-TPO) are found in 80 percent of patients, but the erythrocyte sedimentation rate typically is normal. It is important to distinguish painless thyroiditis from subacute granulomatous thyroiditis (also known as giant cell thyroiditis, subacute thyroiditis, or de Quervain's thyroiditis) and Graves' disease. Painless thyroiditis is distinguished from subacute granulomatous thyroiditis by the absence of thyroid pain and tenderness. Painless thyroiditis is differentiated from Graves' disease by the lack of a thyroid thrill or bruit, ophthalmopathy, pretibial myxedema, and thyroid-stimulating immunoglobulins, as well as by a low or absent rather than elevated radioiodine uptake (11) The term "subacute thyroiditis" is not usually applied to silent, painless thyroiditis with lymphocytic pathological features or to postpartum thyroiditis (4).

Previous studies have rarely reported on the coexistence of subacute thyroiditis and thyroid carcinomas. In most studies, thyroid cancer is associated with granulomatous form of thyroiditis (12-15). The diagnosis of thyroid cancer can be challenging because subacute thyroiditis can result in ultrasound changes that obscure the coexistence of papillary carcinoma.

Our patient presented a typical "silent" (painless) thyroiditis with palpable thyroid nodule. Previous studies have demonstrated that destructive thyroiditis may present as a solitary, palpable nodule with suppressed thyrotropin and should therefore be considered in the differential diagnosis of thyroid lesions (16-18). Nuclear medicine and ultrasound can both be used in the evaluation of patients with destructive thyroiditis. However, ultrasound may be more commonly requested for patients presenting anterior neck pain in order to search for explanations such as acute hemorrhage into a thyroid nodule or an abscess due to infection. In this present case, thyroid ultrasound was performed during the acute phase of thyroiditis because a nodule on the right lobe was felt by palpation.

In fact, subacute thyroiditis can occasionally mimic thyroid carcinoma or thyroid lymphoma due to its hypoechoic appearance in the ultrasound and firmness on palpation. Diffuse hypoechoic change in the thyroid is what made it impossible to differentiate nodular involvement from inflammatory lesion. Therefore, it was recommended to get another ultrasonography examination when the symptoms had resolved and laboratory values have returned to normal in order to rule out an underlying nodular disease (13). Recently, a case of subacute thyroiditis (granulomatous thyroiditis) described a malignant thyroid nodule (0.9 cm) with microcalcification focus found only at control thyroid ultrasound done after clinical and laboratorial recovery (15). Our patient presented a difuse heterogeneous hypoechoic pattern associated with suspicious thyroid nodule. Painless thyroiditis and postpartum thyroiditis may present hypoechogenicity, either diffuse or multifocal, coinciding with each of the episodes of transient thyroid dysfunction that reverted to a normal echographic appearance with recovery of normal thyroid function (19). A diffuse hypoechoic pattern is also seen in Hashimoto's thyroiditis and Graves's disease (8).

In our case, a suspicious heterogeneous thyroid nodule was found on left side by ultrasound, that is, with irregular borders and presence of microcalcification focus (Figure 1) that confirmed papillary carcinoma by histology. Interestingly, it is possible to have a considerable overlap between the ultrasound features of subacute thyroiditis and malignant thyroid nodule. Some studies have demonstrated helpful US indicators for differential diagnosis and it has been considered that a presence of poor defined margin, centripetal reduction echogenicity and no internal vascularity as the most frequent in subacute thyroiditis as malignant thyroid nodules (20). Specimens of painless thyroiditis have shown to be in fact chronic thyroiditis and these histological features indicate that silent thyroiditis may be a form of chronic thyroiditis; for instance, chronic thyroiditis with marked follicular destruction (21). However, studies comparing cancers in thyroperoxidase (TPO) antibody-positive to TPO antibody-negative patients, demonstrated that there was no significant difference in the size, echogenicity, composition, margins, halo presence, calcification presence and type, or vascularity of the cancerous nodule. Among patients with Hashimoto thyroiditis and thyroid cancer, the ultrasound appearance of the cancerous nodule is similar, except that cancerous nodule margins are more likely to be irregular or poorly defined when the gland is heterogeneous (22). These data reinforce that even in the active phase of painless thyroiditis the ultrasound features of thyroid malignancy are preserved and are important clues to cytological analysis.

An interestingly aspect of this case was the presence of microcalcification focus in heterogeneous non-nodular areas in the contralateral lobe (Figure 2). This is in agreement with some studies which have demonstrated that heterogeneous areas with microcalcification focus in the thyroid are clues for the nodular involvement with papillary carcinoma on the initial ultrasound examination of thyroiditis (13). Besides papillary thyroid cancer discovered in thyroid nodule on left lobe, the histological evaluation also found four microcarcinomas on the right thyroid lobe from 0.2 to 0.8 cm of diameter at the corresponding heterogeneous microcalcification areas. These findings reinforce how microcalcifications focus noted in the background of the thyroiditis changes plays a role in raising the suspicion of papillary thyroid carcinoma (13). Interestingly, the thyroid nodule on the right lobe described by palpation and ultrasound (Figure 2) was not confirmed in the histological evaluation. Painless thyroiditis may manifest with transient thyroid nodule probably due to focal or diffuse lymphocytic infiltration (18). In fact, histological abnormalities such as lymphocytic infiltration and follicular epithelial changes of the thyroid, observed in the patients with painless thyroiditis can improve spontaneously during the course of several months (23).

Neck ultrasound is highly sensitive in diagnosing of lymph node involvement by thyroid cancer (15,24). Even with the presence of specific characteristics of malignancy, such as cystic appearance, hyperechoic punctuations, loss of hilum and peripheral vascularization, the diagnosis of cervical lymphadenopathy can be frequently complex (26). In subacute thyroiditis, inflammatory lymphadenopathies are extremely frequent, and enlarged lymph nodes may be described in 66% of patients with this condition (27). In our case a description of round-shaped cervical lymphadenopathy with microcalcification in the central neck (Figure 3) through ultrasound examination was crucial to the suspicion of concomitant thyroid cancer.

In conclusion, thyroid ultrasound is useful for initial evaluation of painless thyroiditis, particularly in patients with palpable thyroid nodule. Therefore, attention should be paid to the complication of papillary carcinoma among patients with this type of thyroiditis, and further cytological examination is recommended in cases presenting with suspect thyroid nodule and/or non-nodular hypoechoic or heterogeneous areas with microcalcification focus.

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