CASE REPORT

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Hashimoto's thyroiditis associated with thyroid adenoma with Hürthle cells – case report

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Abstract

Chronic thyroiditis may present a focal lesion, often-palpable abnormality, simulating nodular disease. The number and morphology of the Hürthle cells (HC) vary in the thyroid aspirate. Distinguishing between neoplastic and non-neoplastic HC lesions is difficult when using the fine-needle aspiration cytology (FNAC). We present the case of a 46-year-old female with a large right nodular goiter and hypothyroidism and high titer of anti-thyroid peroxidase antibody (TPO). The thyroid ultrasound showed a large well-defined nodule (more than 6.8 cm) with hypoechogenicity and microcalcification. FNAC (Mayo Clinic technique) smears revealed HC arranged in flat sheets in 75% in the sample with moderate nuclear pleomorphism, abundant granular cytoplasm showing eosinophilia and well-defined cytoplasmic borders, a lightly eccentric enlarged nuclei; the colloid was reduced and lymphocytes were also described. The final histological examination revealed that oncocyte cell proliferation is limited to the thyroid parenchyma and does not exceed the capsule and has no vascular invasion. The presence of lymphocytic infiltration and a performing FNAC (like Mayo Clinic technique) is absolutely necessary in a focal autoimmune thyroiditis in order to exclude HC carcinoma.

Keywords: Hürthle cells, thyroid adenoma, thyroid cancer, fine-needle aspiration cytology, immunohistochemistry.

Introduction

Lymphocytic thyroiditis, also known as Hashimoto's thyroiditis, appears usually as a diffusely hypertrophic gland that may be of hypoechoic aspect, heterogeneous or a fine micronodular pattern on ultrasound. Chronic thyroiditis may also present as a focal lesion, often a palpable abnormality, simulating nodular disease. The focal form, which may represent a milder or earlier presentation of the disease, may present with focal nodules that prove to be lymphocytic thyroiditis on fine-needle aspiration [1]. The classic definition of Hashimoto's disease includes the triad of lymphocytes, plasma cells, and Hürthle cells (HC) [2–4].

Fine-needle aspiration cytology (FNAC) is the gold standard in the evaluation of thyroid nodules. Occasionally, thyroid aspirates in these conditions consist of HC, known with a real malignant potential. The distinction by cytological criteria between Hürthle cell neoplasm and Hürthle cell adenoma can be a diagnostic challenge [5–8].

Thyroid ultrasound is necessary to identify such a focal thyroiditis nodule that appears to be hypoechoic, with an imprecisely defined contour aspect that is indistinguishable from that of a malignant nodule. The presence of ultrasound a nodular aspect in chronic thyroiditis requires a comprehensive approach, fine-needle aspiration biopsy (FNAB) is mandatory on the opportunity to surgery treatment [8].

HC can be described in benign and malignant tumors, and the pathologist can differentiate them based on the invasion of the capsule and of the blood vessels. The distinction between neoplastic and non-neoplastic HC lesions may be difficult to perform only by FNAC.

We present such a case highlighting that FNAC must be confirmed by histopathology in focal chronic thyroiditis.

Case presentation

In May 2014, a 46-year-old female came to the Department of Endocrinology within the Emergency Hospital of Sibiu, Romania, complaining of a painful right neck swelling for the last two months. Other clinical features included weight gain, palpitations and fatigue for one month, as well as hoarseness in the past two weeks.

The patient had been known with normofunctional multinodular goiter since 2010; between 2010–2014, she did not receive any specialized endocrinology examination or specific hormonal treatment, the function of the thyroid gland being within normal limits, according to the patient's statement. The patient had been previously diagnosed with liver steatosis and dyslipidemia.

The patient did not use to consume alcohol, drugs or medicines that could interfere with the thyroid function; also, she was not a smoker or exposed to any ionic radiations, as she was a housewife.

The clinical examination highlighted an obese person, with a body mass index (BMI) 38 kg/m^2, with a well-

developed adipose tissue in the abdomen region, thighs and face, with palpebral infiltrates. The thyroid gland examination revealed a marked hypertrophy of the right lobe with firm consistency and reduced mobility.

The thyroid hormones evaluation revealed hypothyroid function: free thyroxine (FT4) 0.904 ng/dL (normal range 0.89–1.71 ng/dL) and thyroid-stimulating hormone (TSH) 14 μg/mL (normal range 0.4–4 ng/mL).

The evaluation of the anti-thyroid peroxidase antibody titer showed very high levels: anti-TPO 2230 IU/mL (normal range <35 IU/mL) confirmed the diagnosis of Hashimoto's thyroiditis, while the anti-thyroglobulin antibody titer was normal: 20 IU/mL (normal range <40 IU/mL). Also, the normal calcitonin (<3 pg/mL) (normal range <11.5 pg/mL) excluded a medullar thyroid carcinoma. The thyroid hormones and thyroid antibodies were measured using chemiluminescence immunoassays.

The ultrasound of the cervical region highlighted an enlarged thyroid, with smooth, well-differentiated margins, with a hypoechoic echostructure, intensely heterogeneous, with a rich vascularization. Moreover, in the right lobe, there was highlighted the presence of a hypoechoic, well-differentiated nodule, of approx. 6.8×6.5×4.5 cm, with diffuse microcalcifications in its structure and low vascularization (Figure 1). The parotid and submandibular salivary glands were normal. No revealed laterocervical lymphadenopathy.

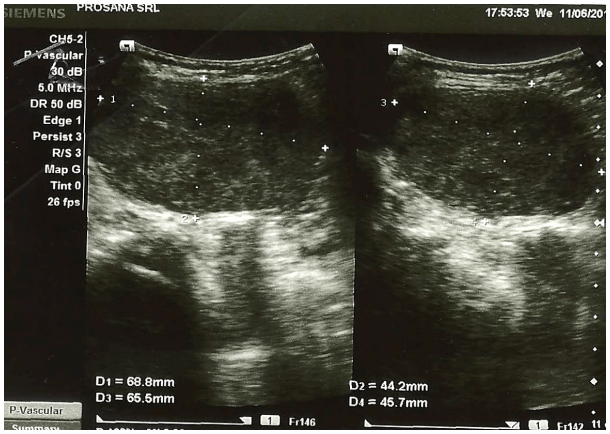

Figure 1 – ***Thyroid ultrasound: a large nodule in the right thyroid lobe, hypoechoic with microcalcifications.***

The radioiodine uptake was performed and showed a low iodine uptake in the right thyroid lobe.

The FNAC of nodule was performed by Mayo Clinic technique, using six 27-gauge needles, cytological material aspirated cells from six different parts of nodule. FNAC smears from the nodule in the right thyroid lobe were cellular, hemorrhagic and comprised HC arranged in flat sheets in 75% in the sample. HC showed moderate nuclear pleomorphism, abundant granular cytoplasm showing eosinophilia and well defined cytoplasmic borders and slightly eccentric enlarged nuclei. Some cells presented prominent nucleoli. The colloid was reduced. In the background blood cells, small groups of follicular cells, inflammatory elements, larger macrophages with "frothy" looking cytoplasm and small eccentric nuclei, were described. Lymphocytes were also described (Figure 2).

There was recommended a surgical treatment based on the compressive feature of the nodule, its big size and the FNAC result.

One month later, the patient underwent a right lobectomy. The surgical excision material was fixed in 10% formalin solution and sent to the histopathology laboratory, where it was processed by paraffin inclusion. For the histopathological diagnosis of the thyroid lesions, there were performed two classical stainings: Hematoxylin–Eosin (HE) and trichrome Goldner–Szekely (GS). Due to the fact that, during the ultrasound examination, the thyroid nodules presented an enlarged volume and diffuse calcifications, there was taken into consideration the possibility of its malignant degeneration. Because of this, for the positive and differential diagnosis, there were performed more immunohistochemical investigations, using the following antibodies:

- anti-thyroglobulin (clone DAk-Tg6, 1:200 dilution, Dako); anti-cytokeratin (CK) 7 (clone M7018, 1:50 dilution, Dako); anti-cytokeratin 19 (clone RCK108, 1:50 dilution, Dako); anti-vimentin (clone V9, 1:50 dilution, Dako); anti-thyroid transcription factor 1 (TTF1) (clone 8G7G31, 1:100 dilution, Dako), for the phenotype characterization of the thyroid nodular parenchymal cells;
- anti-Ki67 (clone MIB-1, 1:50 dilution, Dako) for quantifying the cells in division;
- anti-p53 (clone DO7, 1:50 dilution, Dako) for highlighting potential changes of the TP53;
- anti-CD34 (clone QBEnd10, 1:50 dilution, Dako) for highlighting the microvascular density of the thyroid nodule;
- anti-alpha smooth muscle actin (*α*-SMA) antibody (clone 1A4, 1:100 dilution, Dako) for evaluating the stromal myofibrobalst reaction in the thyroid nodule.

The classical histopathological examination highlighted a deep change of the general structure of the thyroid, by the presence of certain cordons and islands of acidophil cells, unevenly arranged, separated by fine septa of conjunctive stroma. Most of the cells had a polyhedral shape, abundant, granular, acidophil cytoplasm, with large, round nuclei, with a heterogeneously arranged chromatin and 1–2 prominent nucleoli. Some cells presented two and even three nuclei (Figure 3). The cytoplasmic acidophilus of the cells was heterogeneous, being identified the cells with a granular acidophil cytoplasm, and also the intense non-granular, acidophil cells (Figure 4). These oxyphil cells, also called oncocytes or Hürthle cells, represented more than 75% of the thyroid parenchyma cell mass. Quite rarely, there were also identified thyroid follicles, of various sizes, made of both polyhedral cells with acidophil cytoplasm and of cubic cells, similar in shape to the thyroid follicle cells.

The thyroid capsule was not invaded by Hürthle cells (Figure 5), but subcapsularly, there were frequently highlighted inflammatory infiltrates with lymphocytes and plasmocytes that also entered the thyroid parenchyma (Figure 6), thus confirming the diagnosis of Hashimoto's thyroiditis with Hürthle cells.

Frequently, in the thyroid parenchyma, there were identified numerous hemorrhagic suffusions (Figure 7), which shows a special vascular fragility. The classical histopathological data suggested the presence of a thyroid adenoma with Hürthle cells, associated to an autoimmune Hashimoto's thyroiditis.

Knowing the fact that Hürthle cells may be present in Hashimoto's thyroiditis, in thyroid adenomas, and also in thyroid carcinomas (papillary and follicular) for the differential diagnosis of the nodular lesion, there were performed various immunohistochemical investigations.

The use of the anti-thyroglobulin antibody allowed us to observe that most of the cells in the thyroid nodule had a poor reaction, which showed a low secretory capacity of Hürthle cells. The reaction was moderately positive in the thyroid colloid inside the follicles (Figure 8).

Still, the cells of the thyroid nodule were intensely positive to CK7 (Figure 9), CK19 (Figure 10) and partially positive to vimentin (Figure 11).

The evaluation of the proliferative capacity of the cells in the thyroid nodule by using the anti-Ki67 antibody showed that quite a low number (less than 3%) were found in mitoses (Figure 12), and the reaction to the anti-p53 antibody was poorly positive (Figure 13), thus showing that there was not affected gene TP53, also known as the "genome guardian".

The investigation of the thyroid microcirculation in the adenoma, by marking the endothelial cells with the anti-CD34 antibody, showed a normal density of the micro-vessels (Figure 14), and the reaction to α-SMA of the stromal cells was poorly positive (Figure 15), showing that the myofibroblasts of the tumoral stroma, cells responsible for the synthesis of the extra cellular matrix that provides the tumor cell support, were poorly represented.

The post-surgical evolution of the patient was normal, and the thyroid ultrasound performed every semester did not highlight the presence of a local relapse or any significant pathological changes in the left lobe. The TSH and FT4 values were within normal limits, without any hormonal substitution treatment, even though there were expected signs of hypothyroidism after the right lobe extirpation.

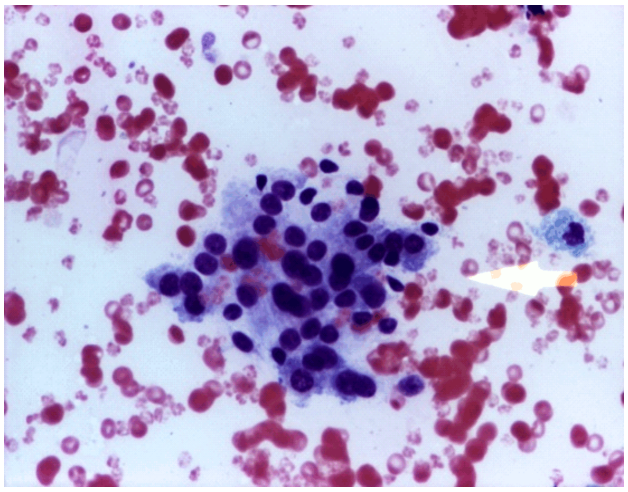

Figure 2 – ***FNAB: Hürthle cells with moderate nuclear pleomorphism, abundant granular cytoplasm and well-defined cytoplasmic borders, eosinophilic and slightly eccentric enlarged nuclei (May–Grünwald–Giemsa staining, ×400).***

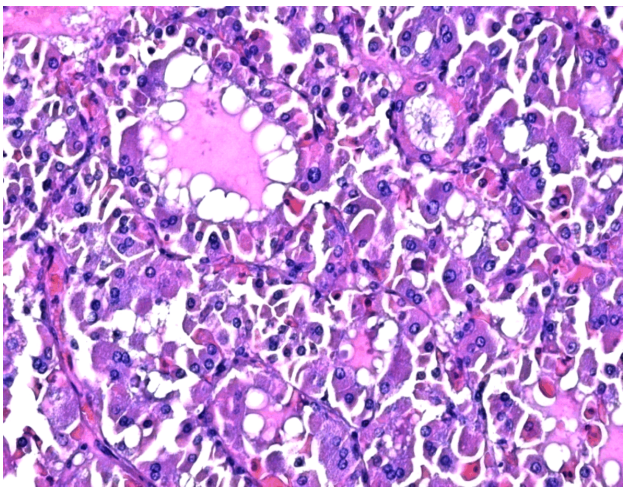

Figure 3 – ***Overall image of the thyroid lobe showing the arrangement of cells as cordons, islands or follicles (HE staining, ×200).***

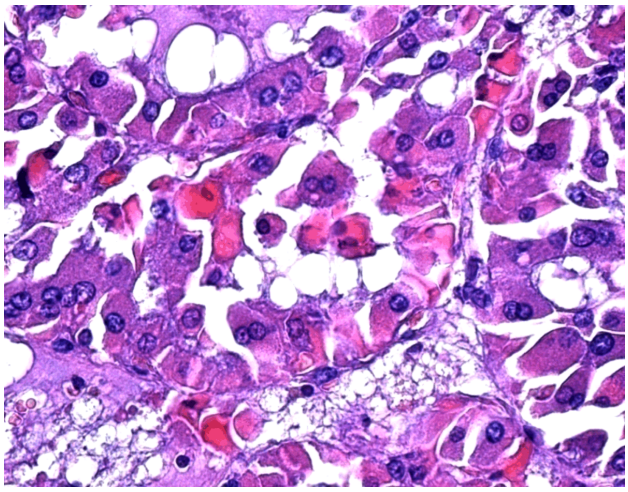

Figure 4 – ***Thyroid parenchyma with one or two nuclei polyhedral cells, with acidophil, granular cytoplasm (Hürthle cells) and intensely acidophil cells with non-granular cytoplasm (HE staining, ×400).***

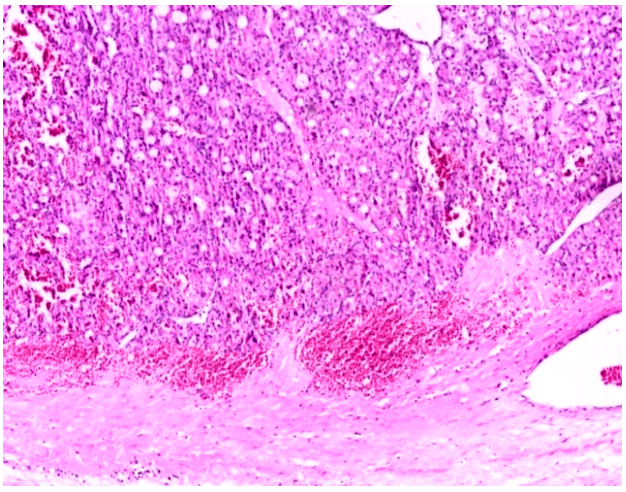

Figure 5 – ***Intact thyroid capsule, non-invaded by Hürthle cells (HE staining, ×40).***

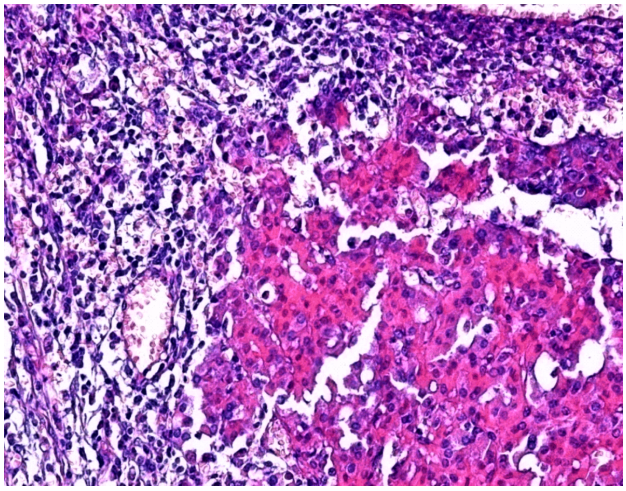

Figure 6 – ***Abundant inflammatory infiltrate, made of subcapsular or intraparenchymatous lymphocytes and plasmocytes, localized among the Hürthle cells (HE staining, ×100).***

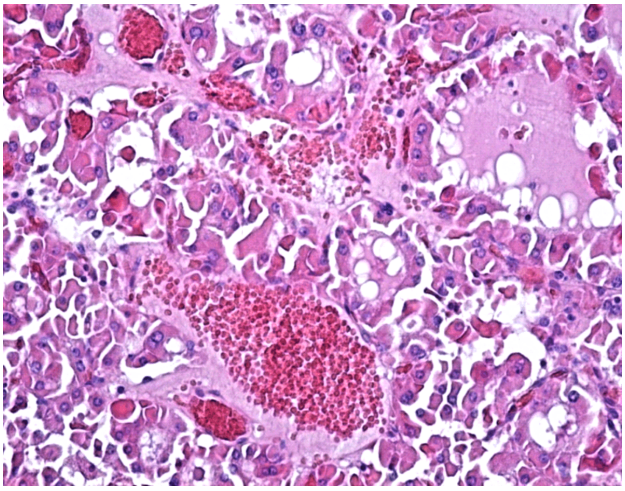

Figure 7 – ***Thyroid tumoral parenchyma with numerous hemorrhagic suffusions (HE staining, ×200).***

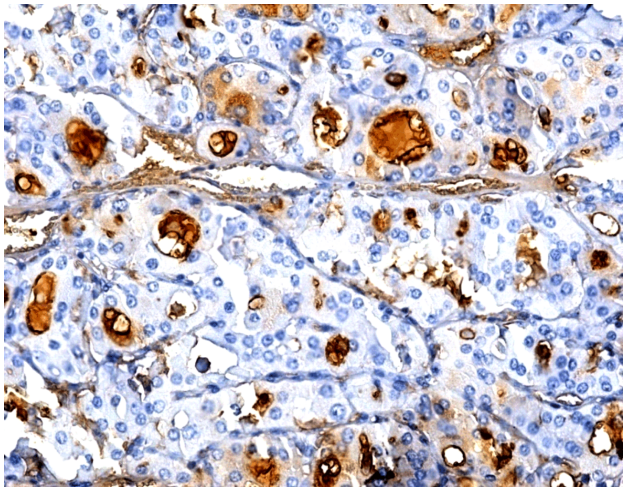

Figure 8 – ***Poorly positive reaction of the Hürthle cells to the anti-thyroglobulin antibody in the thyroid colloid (Anti-thyroglobulin antibody immunomarking, ×200).***

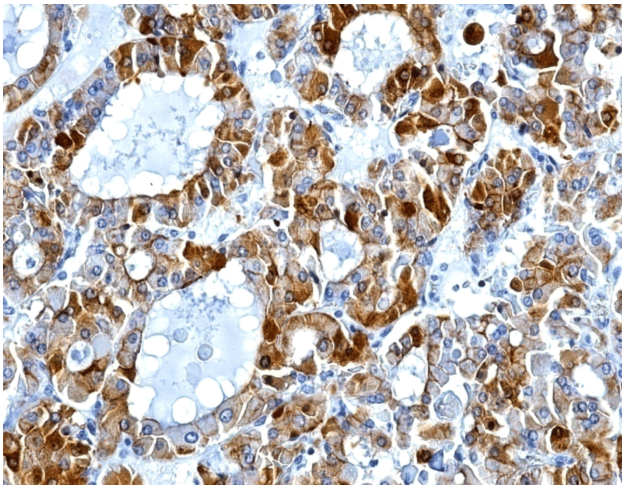

Figure 9 – ***Intense reaction of the Hürthle cells to CK7 (Anti-CK7 antibody immunomarking, ×200).***

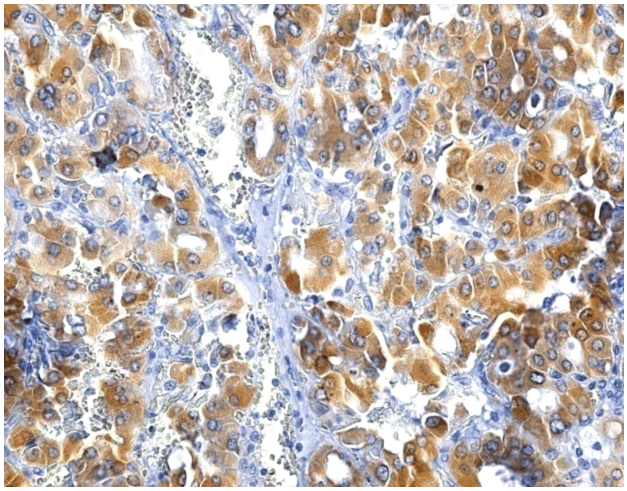

Figure 10 – ***Intense, heterogeneous reaction of the Hürthle cells to CK19 (Anti-CK19 antibody immunomarking, ×200).***

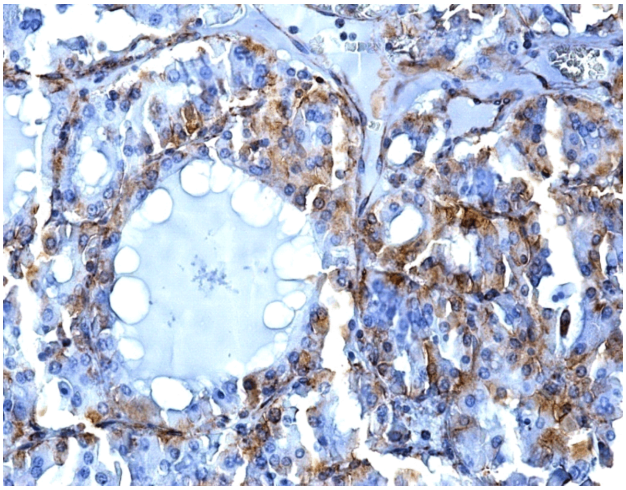

Figure 11 – ***Image of thyroid adenoma with a heterogeneous reaction of the Hürthle cells to vimentin (Anti-vimentin antibody immunomarking, ×200).***

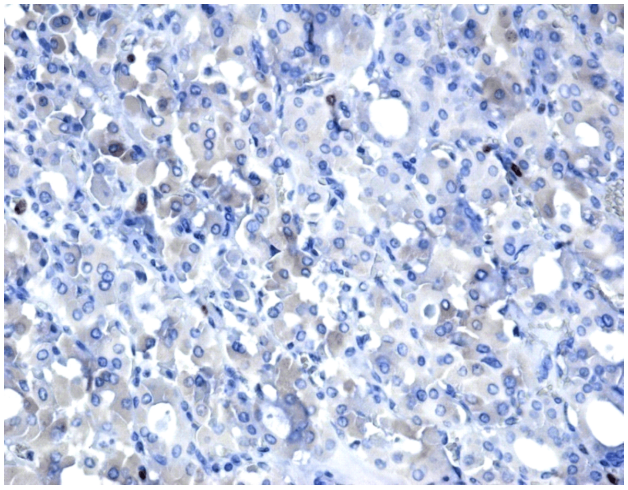

Figure 12 – ***Thyroid adenoma with rare cells positive to Ki67 (Anti-Ki67 antibody immunomarking, ×200).***

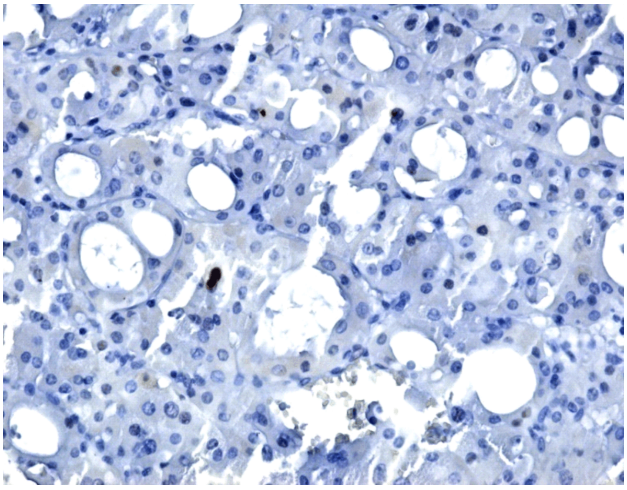

Figure 13 – ***Thyroid Hürthle cells with negative reaction to p53 (Anti-p53 antibody immunomarking, ×200).***

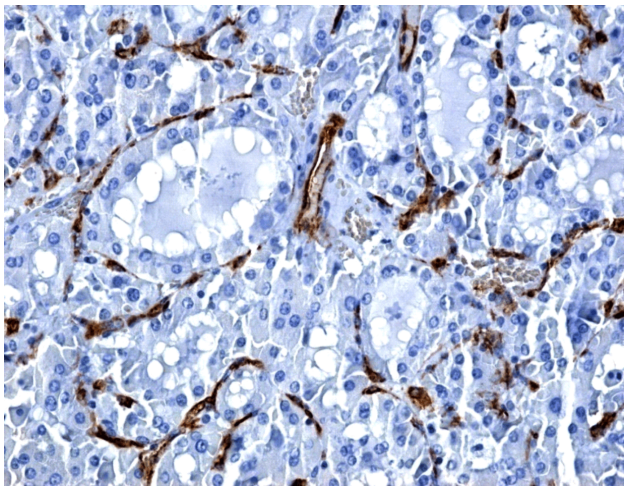

Figure 14 – ***Thyroid adenoma with a normal density of microvessels (Anti-CD34 antibody immunomarking, ×200).***

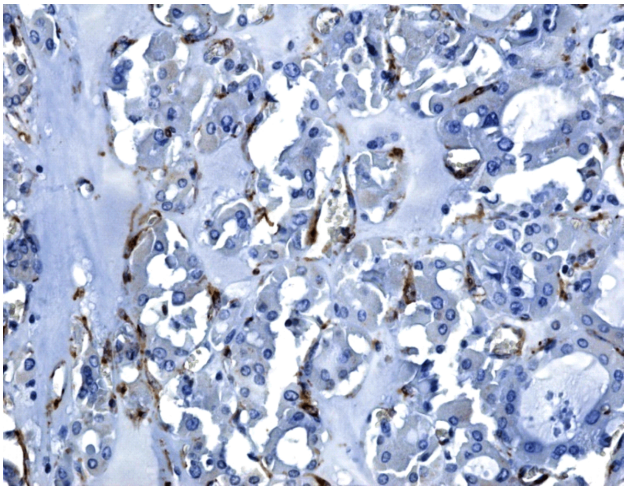

Figure 15 – ***Thyroid adenoma with rare stromal cells positive to α-SMA (Anti-α-SMA immunomarking, ×200).***

Discussion

The thyroid pathology is one of the most frequent pathologies of the endocrine system. It is believed that approx. 200 million people around the world suffer from a thyroid disease [9].

In the last decades, the prevalence of the thyroid pathology increased worldwidely, due to the possibilities of diagnosis opened by the thyroid ultrasound examination, capable of highlighting very low sized thyroid nodules [10–13]. Moreover, the thyroid puncture-biopsy associated with the cytological examination most often allows the establishment of a histopathological diagnosis in over 85–95% of cases [14, 15]. The most frequent detected thyroid lesions are nodular lesions. The thyroid nodules are clinically detected in 5–8% of the population, but their incidence increases up to 15–67% of the population, when it is used the neck ultrasound examination [4]. A multitude of thyroid diseases start or manifest as nodular lesions: nodular goiter, chronic lymphocyte thyroiditis, thyroid ultrasound, papillary carcinomas, medullary carcinomas, etc.

In our study, the thyroid ultrasound highlighted the presence of two distinct lesions: a hypoechoic thyroid nodule in the right lobe, with diffuse calcifications, which raised the suspicion of a thyroid neoplastic process and a heterogeneous hypertrophy of the rest of the thyroid, with an abundant vascularization that suggested the presence of thyroiditis. FNAC and the serological markers allowed the diagnosing of a Hashimoto's thyroiditis with a high number of Hürthle cells.

A focal thyroiditis can hide in some cases an oncocytoma. Thyroid oncocytomas are rare tumors, but they can be aggressive. The ultrasound is the first investigation performed to identify such nodular forms of chronic thyroiditis. If the thyroid ultrasound is suspicious, FNAC is important to complete the investigation [16]. Our case emphasized the importance of the ultrasound-guided FNAC to demonstrate a predominance of HC suspicious for HC neoplasia (HCN).

Adequacy of FNAC has been variably defined as a minimum of six groups of follicular cells containing 10 (benign) cells per group on one or more slides, five to six groups of follicular cells with 10–20 cells per group on at least two slides, and six groups on at least two of six aspirates [17]. The *Bethesda Guidelines* specifically define a satisfactory specimen as containing six groups

of benign follicular cells, each group composed of 10 cells. Exceptions to this requirement do exist, as in the case of smears containing abundant colloid and few cells, which may be interpreted as benign [18–20].

Some laboratories interpret an aspirate containing 50% HCs as suspicious for HCN, whereas others require a far more stringent 90%. A commonly used definition, and that preferred by the authors, is an aspirate containing 75% HCs with little or no background colloid; the nuclear features of papillary thyroid carcinoma (PTC) must be absent [2].

Using the 75% criterion thus selects for those nodules more likely to harbor malignancy. Because it is impossible to identify the presence or absence of a capsule on FNAB, all lesions meeting these criteria should be treated as HCNs and patients should undergo thyroid lobectomy for diagnosis, with the knowledge that a substantial percentage will prove to be non-neoplastic (15%–25%, up to 35% in some series) on final histology. Malignancy will be found in up to 30%, and the remaining nodules will be benign adenomas [5, 21, 22]. Several studies have reached contradictory conclusions regarding the value of specific cytological findings in these lesions [23, 24].

In our patient, according to the cytological guidelines, we concluded that there was no suspicion of malignancy (FNAC with an aspirate containing less 75% HCs with reduced colloid).

A mixture of Hürthle cells and normal follicular epithelial cells is more consistent with a hyperplastic nodule. Hürthle cells may show nuclear pleomorphism. Nuclei tend to be more uniform in size in HC tumors than Hashimoto's thyroiditis. In one case, Chandanwale *et al.* described HCs with moderate nuclear pleomorphism, but normal thyroid follicular cells were not seen in the aspirate [8, 23, 24].

In our case, the cytological exam showed moderate nuclear pleomorphism of HC, abundant granular cytoplasm and well defined cytoplasmic borders. Prominent nucleoli were also described in some cells. All of these elements described a clear diagnostic of a chronic inflammation. However, the nodule size and the compression phenomena correlated with a relatively high proportion of HC compelled us to recommend the surgical removal of the nodule.

The study of 14 cytological features by Elliot *et al.* showed: overall cellularity, cytoarchitecture, percentage of Hürthle cells, percentage of single Hürthle cells, percentage of follicular cells observed as naked HC nuclei, background colloid, chronic inflammation, cystic change, transgressing blood vessels, intracytoplasmic lumina, multinucleated Hürthle cells, nuclear to cytoplasmic ratio, nuclear pleomorphism/atypia and nucleolar prominence [7, 8]. Out of the 14 features, non-macrofollicular architecture, absence of background colloid, absence of chronic inflammation and presence of transgressing blood vessels were statistically significant in predicting HC neoplasm in 86% of HC lesions. They found 90% HCs and >10% single HC in cytology smears of HC neoplasms [7, 8].

In our case, thyroid aspirates consisted of HC and lymphocyte was seen lying in HC sheets and supported us in diagnosed of Hashimoto's thyroiditis.

In most cases, making a clear distinction between neoplastic and non-neoplastic HC lesions may be difficult. Prominent nucleoli are commonly seen in non-neoplastic HC lesions [8]. Similar findings were occasionally seen in our case.

One study observed that some cases of non-neoplastic HC proliferations in Hashimoto's thyroiditis mimic suspicious/follicular neoplasm of HC type on cytology [22]. Disorganized and poorly cohesive masses of oxyphilic cells with prominent nucleoli are more indicative of a neoplastic lesion. The presence of HC and lymphocytes was seen in hyperplastic lesion [23]. We described such association between HC and inflammatory elements also in our case. Failure to demonstrate lymphocytes and to appreciate non-neoplastic nature of HC in cytology smears, often results in misdiagnosis of HC neoplasm [24].

Classically, the FNAC was considered a good predictor of HC non-neoplastic lesion but has little diagnosis value in evaluating the neoplastic HC lesions, since for a tumor to be deemed malignant there has to be vascular or capsular invasion. The majority of thyroid FNAC that demonstrate a predominance of HCs are diagnosed as suspicious for HCN. As a result, in a large series, less than 10% of patients with FNA samples diagnosed as suspicious for a HCN were found to have HC carcinoma at the time of resection [25].

In our case, occasional lymphocyte in HC sheets in correlation with high value of TPO established the correct diagnosis of Hashimoto's thyroiditis. Chandanwale *et al.* recommended a careful search of lymphocytes in HC sheets on FNAC smears, multiple aspirates, associated with clinical findings and ancillary techniques to reduce the diagnostic pitfall and avoids unnecessary surgery [8].

In our study, the problems of positive and differential diagnosis were raised by the right lobe, as, by its size and ultrasound aspect, it could be a thyroid carcinoma. Various studies showed that thyroid nodules larger than 4 cm present a high malignant risk [26, 27]. The classical histopathological examination performed by us did not highlight any characteristic nuclear changes of the thyroid tumor cells, but the presence of Hürthle cells [called oncocytes by *World Health Organization* (WHO)] in a very large number preserved the suspicion of malignant degeneration, especially due to the fact that there is a particular form of papillary cancer, called oncocytic. The Hürthle cells are non-specific to a certain pathology, thus they may be found both in tumor thyroid lesions (adenomas, carcinomas), and also in non-tumoral ones [2, 4, 28].

The immunohistochemical study performed by us showed that the tumoral cells had a low proliferation rhythm, less than 3% of the HCs being positive to the anti-Ki67 antibody. It is well known the fact that the Ki67 marker is correlated to the stage of differentiation, invasion and metastases. Various studies showed that there are significant statistical differences between the immunohistochemical reaction of the Ki67 marker between the thyroid carcinoma and adenoma [29, 30].

Also, we showed that the TP54 gene was not altered, quite a few cells having a positive reaction to the anti-p53 antibody. The data we obtained are correlated to other studies showing that the reaction to the marker is low in the tumoral lesions with a low aggressiveness [31].

The immunohistochemical reaction of the tumoral cells to CK7 and CK19 confirmed the follicular origin of the Hürthle cells, but, according to various studies [32–34], the two cytokeratins are positive both in the malignant thyroid lesions and in the benign ones and they cannot be used as a differential diagnosis.

Although they have a follicular origin, in our study, the HCs had a low immunohistochemical reaction to the anti-thyroglobulin antibody, which shows a low synthesis and secretion capacity of the thyroid hormones.

The histological and immunohistochemical aspects confirmed the clinical, paraclinical, imagistic and cytological diagnosis, thus identifying a Hashimoto's thyroiditis associated to a thyroid adenoma with Hürthle cells.

Conclusions

We can say that the identification of benign form or malignant forms of HC neoplasms is a difficult process in which an important role is played by the FNAC; in suspicious cases, it should be completed by final histopathology examination. An oncocytic nodule in chronic lymphocytic thyroiditis may be completely encapsulated and show no evidence of capsular or vascular invasion. In the absence of nuclear features of papillary carcinoma in FNAC, this would be considered an adenoma and a lobectomy is recommended to be performed if the nodule is larger than 4 cm and is compressive, and after a thyroid ultrasound follow up is necessary.

Conflict of interests

The authors declare that they have no conflict of interests.

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