

HISTOLOGICAL CHANGES IN BENIGN SOLITARY THYROID NODULES — A PROSPECTIVE MORPHOLOGICAL STUDY

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Abstract

Background: The solitary benign thyroid nodules represent one of the most common abnormalities affecting the thyroid gland. The appearance of solitary thyroid nodules is variable and all the patients should be assessed as soon as possible in order to establish the benign nature of the lesion and to rule-out malignancy.

The aim of the present study is to show the histological changes that appear during evolution of benign solitary thyroid nodules and rapid growing rate along 6 years, in 71 patients (65 women and 6 men).

Methods: All cases were evaluated by clinical, ultrasound, biochemical (at every 6 months) and FNA (initially and repeated between 10 months and 4 years afterwards); 26 out of 71 presented, along evolution, an increase of thyroid nodule (24 women and 2 men) from 1.77 cm diameter (1.4-2 cm) to more than 2.5 cm (2.5-4.3 cm), therefore a radical surgical attitude was performed.

Results: Histological postsurgery data showed degenerative changes in all cases, with repetitive nodular hemorrhage (26 cases), sclerohyalinisation of the interfollicular stroma (4 cases), cholesteatoma (5 cases) and inflammatory infiltrate (8 cases).

In conclusion, the significant growth of a benign solitary nodule is determined by repetitive hemorrhages in the thyroid tissue. The associated sclerosis induces changes in the nodular firmness and might trigger the thyroid surgery.

Key words: solitary benign thyroid nodule, long-term conservative follow-up, fine-needle aspiration, repetitive nodular hemorrhages, stromal sclerohyalinisation.

INTRODUCTION

The nodular thyroid is the most frequent endocrine disease in clinical endocrinology and the nonfunctional benign solitary thyroid nodule is the most frequent pathological abnormality of the thyroid gland.

Some authors have revealed that the appearance of thyroid nodules depends on age, sex, iodine, cervical irradiation, smoking habits and fertility status (1). The

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socio-economic and professional factors appear to have an important role in the pathogenesis and evolution of thyroid nodules. Thus, subjects submitted to stress or a long period of efforts are more likely to develop this condition (2).

Studies on mono- and dizygotic subjects suggest that genetic factors can be involved in the pathogenesis of thyroid nodules, the genetic abnormality of ATPO, of 2p24-25 chromosomal locus (3) or an inadequate expression of Na/I symporter (4) could have an important role in the etiology of cold nodules.

The management of the nonfunctional solitary thyroid nodules without malignancy is multidisciplinary involving in the first instance the endocrinologist, radiologist and pathologist. The mainstone of diagnosis is FNAB which decides the malignancy or conservative attitude. In patients followed-up long term conservatively only with regular check-ups without any other medical treatment, it was observed that these benign solitary nodules can increase significantly in size, sometimes in a short time period. This requires a re-assessed of the case and a new therapeutic attitude.

The aim of the present study is to discover the main histological changes that appear at the level of benign solitary thyroid nodules with an unfavorable evolution, manifested by the increase in volume (over 2.5 cm), detected by clinical and ultrasonography follow-up.

PATIENTS AND METHODS

A prospective follow-up along 6 years was performed in 71 patients with benign solitary nonfunctional thyroid nodule in which the initial FNA did not raise the suspicion of a malign lesion. Inclusion criteria were: age between 18 and 69 years, with a single thyroid nodule seen at US, with initial diameter above 1.7 cm. Exclusion criteria were: certified hyperthyroidism or thyroid autoimmunity, pregnancy, and thyroid malignancy. All these have been diagnosed and monitored at our medical centre. Among these were selected the patients registering an unfavorable evolution, in a time between 1 and 4 years from the beginning of the monitoring, ascertaining the increase of the size nodule. This represented the study

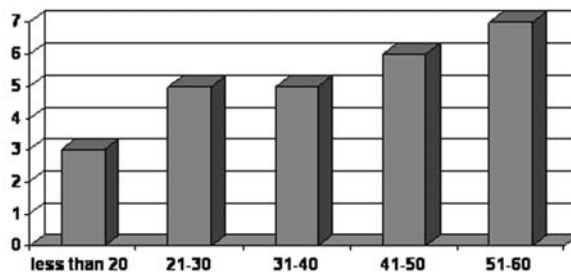


Fig.1. Distribution of patients with ages.

group, while the rest up to 71 were the control group.

The study group included 26 patients from the initial cohort of 71: 24 women and 2 men, aged between 18 to 59 years at the moment of their initial diagnostic and with a homogeneous repartition on decades (Fig.1), without significant personal disease history, without irradiation in the cervical area, but with an activity which imposed an accelerated life style and chronic or repeated psychic stress conditions.

In all the 26 cases the thyroid nodule was observed due to rapid increase in a short time, being observed by the patient or the entourage in a period between 1 and 6 weeks, requiring the first visit to the endocrinologist.

All the cases studied followed the same protocol: clinical examination, thyroid ultrasonography, measurement of serum TSH and FT4 levels and FNA.

The clinical examination of twenty-six cases revealed the presence of a solitary nodular tumor in the right thyroid lobe in 17 cases, in the left thyroid lobe in 8 cases and in the thyroid isthmus in 1 case. All of these cases presented with a diameter between 14 to 20 mm and with variable consistency (from soft to firm), but without adherence, mobile and without cervical lymph nodes. The thyroid ultrasonography (US) confirmed the results of the clinical examination, showing a solitary nodule. The initial US was:

- hypodense, partially cystic (12 cases)
- hypodense (5 cases)
- predominantly cystic (4 cases)
- hypodense with densification areas (3 cases)
- solid with microcalcifications (2 cases)

It must be mentioned that some of the nodules felt were of sizes lower than the ones shown at the US. The thyroid function was normal in all patients, confirmed by measurements of TSH (1.57 mUI/L between 0.7-2.7 mUI/L) and freeT4 (13.5 pg/mL, between 8.5-15.92 pg/mL). The FNA indicated normal cellularity, excluding signs of malignancy, with colloid, recent hemorrhages or siderophage fields. In 11 cases the FNA allowed the complete emptying (4 cases), quasi-complete (5 cases) or partial (2 cases) of the cystic lesion. Taking into account the clinic context, the results of the investigations performed and the patient's option, all cases were clinically, hormonally and ultrasonographically monitored, the controls being made every 6 months.

At each follow-up, patients were questioned on the possible appearance of symptoms connected to the nodule or beginning of a thyroid dysfunction. The clinic examination followed the dimensions of the nodule, consistency, its mobility and the loco-regional lymph nodes. During this conservative long-term (6 years) follow-up period, the thyroid function was normal in all patients, confirmed by TSH measurement (1.45 UI/ml, between 0.9-2 UI/mL, before surgery).

In all the 26 cases the sole element that kept the attention during the monitoring was the increase in dimensions of the nodule highlighted in the clinic and ultrasonographic examination. At a variable period of time (12-48 months), the clinic and ultrasonographic control has shown the increase in size of the nodule (diameter ultrasonographic over 2.5 cm in 6 cases, over 3 cm in 16 cases, over 3.5 cm

in 3 cases and over 4 cm in 1 case). In some cases growth was also associated with the change in consistency. The developing character of the nodule in these patients triggered a reassessment of the diagnosis to exclude a possible malignant transformation of the thyroid lesion and a new FNA was performed.

None of the patients revealed elements suggesting a malignant transformation of the thyroid lesion. In all cases, the FNA indicated normal cellularity, without malignant signs. Invariably, the nodular lesions were characterized by normal follicular epithelium filled with fresh haematic pigment. Variable amounts of colloid, cholesterol crystals, interstitial sclerohyalinisation and perifollicular inflamed infiltrate were present as well. The growth in dimensions of the thyroid nodule triggered the reassessment of the therapeutic attitude, indicating the surgery intervention. The type of surgery intervention was lobectomy with isthmectomy.

In all the operated cases an extemporaneous examination and paraffin block were performed. The sections were stained with hemalaun-eosin and examined at the microscope with visible light.

RESULTS

The microscopic examination of the thyroid specimen highlighted encapsulated lesions with respect to the normal thyroid tissue. No capsule invasion phenomena were noticed. From a pathology perspective all cases have proven to be benign thyroid lesions with degenerating phenomena. At the level of the nodule the glandular parenchyma appeared organized as small follicles with a variable aspect, from flattened cells to tall cells, showing a variable functional activity. The mitoses were absent.

The most frequent histological changes were:

- intrafollicular and interstitial hemorrhages;
- necrobiosis areas with accumulation of cholesterol crystals;
- sclerosis- hyalinization at the level of the interstitial areas.

However, the most frequent lesions were the recent and old intrafollicular and interstitial hemorrhages, some with limited microhaemorrhages, others with massive hemorrhages. The microhaemorrhages are characterized by red blood cells located in the follicular colloid (Fig.2). These might be facilitated by the presence of a discontinuous epithelium which can be present in some follicles (Fig. 3). In massive hemorrhages the thyroid follicles are small and appear as “drowned” or surrounded by red blood cells while the nuclei of thyrocytes have hypoxic changes (Fig. 4). In recent hemorrhages the red blood cells are admixed with the colloid. The interstitial areas are intact and siderophagia is missing. In older hemorrhages siderophagia is present in follicular epithelium. Some cells remain attached to the follicular epithelium, while others are separated from the epithelial wall and appear in the follicular lumen (Fig. 5).

The presence of fresh and haematic pigments of different metabolic stages suggests repetitive hemorrhages in the lesion (Fig. 6). In addition, the old haemorrhages are characterized by multifocal haematic pigment deposition (Fig. 7).

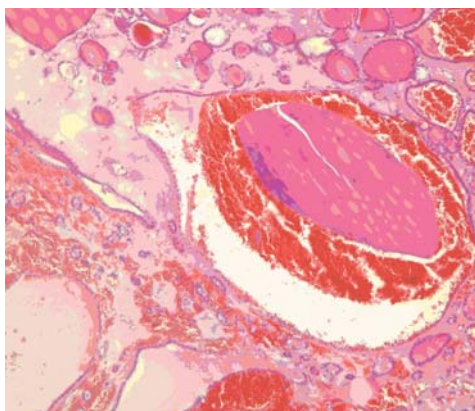


Figure 2. Recent intrafollicular microhemorrhages with enlargement of thyroid follicles. Microhemorrhages are also present in the interstitial tissue. HE stain

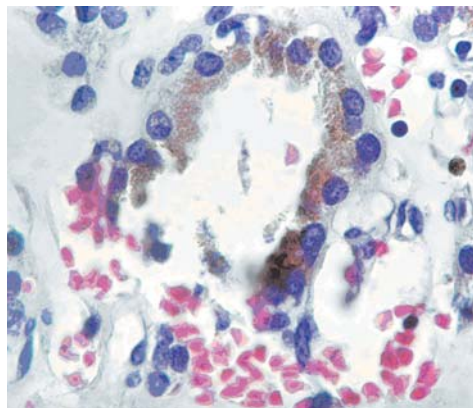


Figure 3. Siderophagia in follicular epithelium. Disruption of epithelial follicular wall with the invasion of colloid by red cells. HE stain

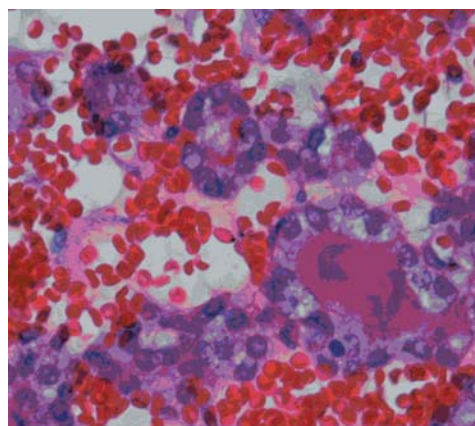


Figure 4. Recent massive hemorrhages with small follicles surrounded by red cells and nuclear changes of thyrocytes. HE stain

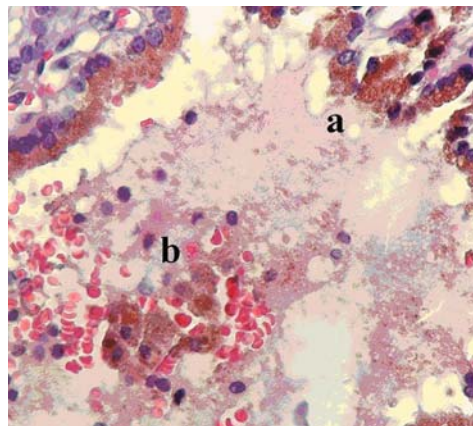


Figure 5. Follicular epithelium with siderophagia. **a.** Siderophages attached to follicular epithelium hypoxic thyrocytes ("in situ") **b.** Siderophages separated from the epithelial wall. HE stain

Interestingly, we have been able to describe in some cases a concentric pattern of siderophagia. This adds up to areas of intrafollicular haemorrhage and ultimately results in a significantly increased size of the nodule (Fig. 8). In some microscopic fields cholesterol crystals were identified in the background of a dense sclerohyalinisation mimicking "pseudo" granulomatous lesions (Fig. 9). The process of sclerohyalinisation was extensive in some cases involving the interfollicular areas (Fig. 10). Rare, haemorrhagic necrotic areas with "shadows follicular cells" were present in some nodules (Fig. 11).

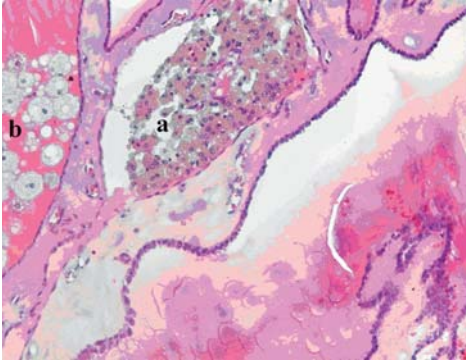


Figure 6. Different ages of siderophagia.
a. Recent haematic pigment. **b.** Haematic pigment in different metabolic stages. HE stain

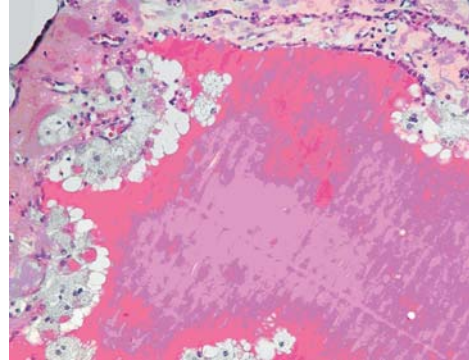


Figure 7. Multicentric marginal siderophagia starting in follicular epithelium. HE stain

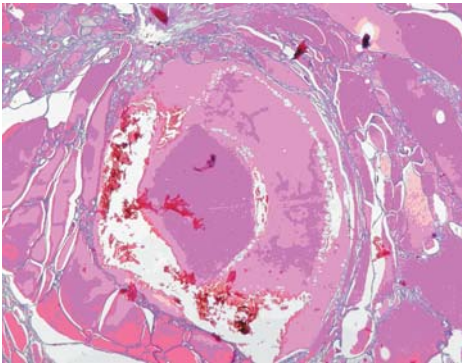


Figure 8. Recent and middle-aged intrafollicular hemorrhages with enlargement of thyroid follicles. HE stain



Figure 9. Cholesterol crystals and periphery sclero-hyalinisation process. HE stain

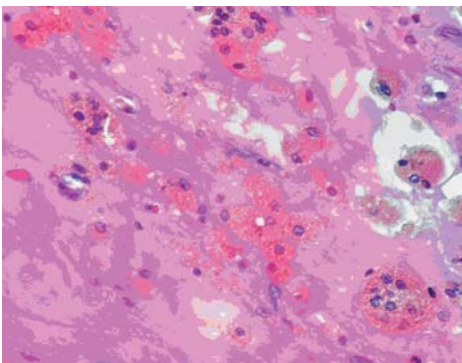


Figure 10. Recent siderophagia and incipient sclero-hyalinisation process. HE stain

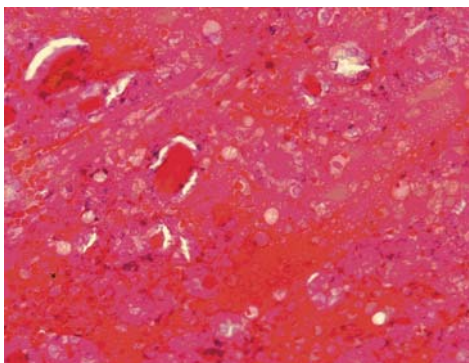


Figure 11. Hemorrhagic necrotic areas with "shadows follicular cells". HE stain

DISCUSSION

In our study we have chosen one of the most frequent thyroid diseases in the endocrinology service - solitary thyroid nodule. Its purpose was to follow which are the main lesions that can determine the unfavorable evolution of a solitary thyroid nodule, when, based on the investigations performed, the suspicion of malignancy was removed.

The incidence of palpable thyroid nodules in adult population is about 4-7%, representing about 10-18 million people in the world (5). They can be detected by the patient himself, or as a result of a clinical examination. In many cases the nodules of the thyroid gland are detected by ultrasonography performed for other reasons. Up to 70% of adults have visible nodules in thyroid ultrasonography, the majority under 1 cm in diameter, undetected by palpation of the thyroid gland, even those situated in the anterior region of thyroid lobes (6). Overall, about half of thyroid nodules detected by ultrasonography are not identified by clinical examination (7). It is worth mentioning that about 20% of patients with a palpable nodule have in fact a multinodular goiter with one dominant nodule (8,9).

If in the past it was considered that the incidence of thyroid nodules grows with the age, especially in women, it is presently ascertained that, although a high frequency remained favorable in women, the lower limit of the presenting age was seriously reduced, and the incidence of thyroid nodules in younger persons is growing (10,11). This aspect could also be observed in our study, about 30% of studied cases being observed in patients under the age of 30.

Over the last few years, authors reported a considerable reduction of the time between the appearance of a nodular lesion and the first medical examination. Most of solitary thyroid nodules do not cause symptoms but, in some cases, patients report cervical pressure or pain, suggesting a spontaneous intranodular hemorrhage. However, it is the general assumption that a solitary fast growing thyroid nodule could represent a malignancy which determines the patient to seek medical attention (12). In all our studied cases the reason for coming to the endocrinologist was the recent appearance of a solitary thyroid nodule.

Epidemiological data indicates that most of the solitary non-functioning thyroid nodules are benign. The malignancy ratio in solitary nodules and multinodular goiters was considered to be between 6.3% (13) and 22.5% (14). The risk for thyroid cancer is similar in patients with 1 or 2 nodules larger than 1 cm and decreases with the number of nodules (3 or more). The malignancy risk is increased in cases of solitary firm nodule with punctiform calcifications, especially in men (15).

However, a patient presenting with a solitary thyroid nodule requires a very quick diagnostic, to establish the nature of tumor and the presence of possible risk factors for malignancy. The most frequent morphological abnormalities described under the category of solitary thyroid nodules are colloid nodules, follicular adenomas, nodular hyperplasia and inflammatory lesions (16).

The initial assessment of a thyroid nodule includes: thyroid ultrasonography, FNA, thyroid hormonal profiles and, in certain cases, immunocytochemistry (17).

However, there is no single “gold-standard” method which could distinguish between the benign and malignant nature a thyroid nodule before surgery (18).

Patients from our study have followed the same investigation protocol that consisted, together with the case history and the clinical examination, of performing thyroid ultrasonography that confirmed the existence of a single thyroid nodule and provided information on the echographic characters of nodular lesion, the thyroid fine-needle aspiration that excluded the existence of elements raising the suspicion of a malignant lesion and the thyroid hormonal profile that confirmed the state of euthyroidism. Thyroid scintigraphy was not recommended in any of our patients because epidemiological data have indicated that only 5-15% of the hormonal and scintigraphically nonfunctional thyroid nodules are neoplastic processes (19). The thyroid scintigraphy is reserved to the patients with suspicious or nondiagnosticable cytology on FNAB or to the patients with solitary thyroid nodule and low TSH, to make the difference between a toxic adenoma and a cold nodule from Graves' disease (20). The management of patients diagnosed with single thyroid nodules is multidisciplinary including an endocrinologist, a pathologist and a radiologist. The cases with borderline assesseds will undergo surgery (21) whereas those with benign cytological profile will be recommended suppression hormonal therapy, sclerotherapy with alcohol (22, 23) or the recent ultrasound-guided interstitial laser photocoagulation (24, 25). A large number will be followed long-term with only regular check-ups.

The suppression treatment with L-Thyroxine is still controversial. Most of benign thyroid nodules do not respond to hormonal therapy. Many of them remain at the same dimensions and have the same benign character for a long period of time. Some of them undergo spontaneous decrease in size, with the complete regression of the nodule (26). The response to the suppression therapy is influenced by the dimensions of the nodule, better for nodules under 2.5 cm and by the cytological characteristics of the nodule, the small and the colloidal nodules being more sensible to treatment than fibrotic or hyperplastic nodules. Patients with exclusive or dominant solid nodule respond much better than the patients with cystic nodules (27). Also, the patients with higher TG level respond, usually, better to the suppression treatment (28). It is considered that only 10-20% of patients with solitary thyroid nodules and benign cytology have a good answer to the suppression therapy (29). In addition, the suppression treatment must be very well motivated and followed-up because a long term administration of L-Thyroxine can cause side effects on the cardio-vascular and skeletal system (30).

Starting from the clinical context, the results of the investigations performed and the patient's option, our patients did not receive a suppression treatment; they have simply managed by regular check-ups in which the general features of the nodules are assessed by clinical follow-up and ultrasonography; in addition, since most of our patients were women, this would add a supplementary risk factor for osteoporosis. During the entire period of monitorisation all patients remained euthyroid. The subsequent investigation showed the dynamic nature of the nodule. All 26 patients have reached an increased size of the nodule in a 1-4 years interval, associated in some cases with the tissue firmness. None of the other worrisome signs were present in any of the patients. While useful, thyroid US could not establish a differential diagnostic

between an intrafollicular hemorrhage and a possible malignant lesion. However, ultrasound-elastography, a newly developed imaging technique, seems to have great potential as a new means for the differential diagnosis between benign and malignant tumors. Combined with other US modalities, elastography, which provides an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force, can help to identify thyroid nodules that are likely to be malignant (31).

In the absence of elements of malignancy, the completion of the assessment of these patients requires additional FNAs. In none of the cases studied there were obtained elements suggesting a malignant transformation of the thyroid lesion. Taking into account the large size of the nodule and the impact of its increase on the patient's mental condition, it was decided to direct the therapy towards the surgical treatment.

Some surgeons consider that the election approach for the solitary benign thyroid nodules is the lobectomy, while others indicate lobe - isthmectomy (32). The lobectomy in these cases has the risk of relapse. After 4 years from the lobectomy, without thyroid substitution treatment, the relapse was present in almost all cases with nodular hyperplasia (33). The lobectomy with isthmectomy was performed in all the cases studied by us, having the advantages of lower degree of post-surgery complications and a smaller period of hospitalization. All the patients were submitted to thyroid treatment post surgery.

The significant increase in size of the nodules in our study could be explained by degenerative changes. These were identified in the thyroid follicles and also in the interfollicular spaces. The most frequent histological changes were the intrafollicular and interstitial hemorrhages. Necrobiotic areas and cholesterol crystals have been observed as well. In some cases old hemorrhages were associated with a sclerothyalinisation of the interfollicular stroma. The repetitive hemorrhages in the thyroid tissue can induce the growing of the nodule and the sclerothyalinisation process can produce changes in its firmness.

CONCLUSIONS

Patients with solitary thyroid nodule in which the malignancy has been ruled-out, with a recent increase in nodule size, must be reevaluated by FNA. The most frequent lesions in benign nodules are intrafollicular and interstitial hemorrhage. Repetitive hemorrhages are responsible for the enlarging of the nodules, while the sclerothyalinisation process induces changes in firmness, an unfavorable evolution of the benign solitary thyroid nodule imposing surgery.

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