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ORIGINAL ARTICLE

Complex thyroid nodules with nondiagnostic fine needle aspiration cytology: histopathologic outcomes and comparison of the cytologic variants (cystic vs. acellular)

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Abstract Management of complex thyroid nodules (CTN) is a common dilemma due to their high prevalence and frequent nondiagnostic fine needle aspiration cytology (FNAC). In order to know the rate of malignancy, we reviewed our experience about histopathologic diagnosis of CTN with nondiagnostic FNAC, and we analyzed if cytological variants of nondiagnostic FNAC indicated different histopathologic outcomes. We conducted a review of 927 consecutive aspirations performed between 2003 and 2008. We selected patients without history of radiation, with echographic CTN, and nondiagnostic FNAC, who underwent surgery. We analyzed histopathologic results and compared patients with benign and malignant nodules, and searched for differences between patients with cystic changes in FNAC (C-FNAC), and patients with acellular or only bloody FNAC (A-FNAC). Thirty-six patients were included (mean age 45.7 ± 13 years; 30 females). Four patients had malignant nodules; all were papillary carcinomas. Patients with benign nodules had a similar profile to patients with malignant nodules. Patients with C-FNAC ($n = 21$) were younger (41.3 ± 12.6 vs. 51.8 ± 11.2 years; $P < 0.02$), had more lymphocytic thyroiditis (33.3 vs. 0%; $P < 0.02$), a slightly higher rate of carcinoma in the nodule (14.3 vs. 6.6%; *P*: ns), and also of papillary microcarcinoma outside the nodule (9.6 vs. 0%; *P*: ns) than patients with A-FNAC. In conclusion, we report an 11.1% malignancy rate in CTN with nondiagnostic FNAC. Nodules with C-FNAC variant had a slightly higher rate of malignancy than A-FNAC, which may be in relation with younger age and higher prevalence of lymphocytic thyroiditis in this group of patients.

Keywords Thyroid nodule · Fine needle aspiration biopsy · Thyroid neoplasm

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Introduction

Nodular thyroid disease is considered to be a common clinical problem but its diagnosis and management have remained controversial for more than two decades [1–5].

Thyroid nodules are solid or complex (mixed solid and cystic in variable proportion) [5]. True thyroid cysts without a solid component are rarely found in thyroid glands [1, 6–8], so frequently "cystic nodule" is used as "complex nodule." Complex thyroid nodules (CTN) account for about one-third of all palpable thyroid lesions [1, 3]. The prevalence of echographic CTN, palpable and non-palpable, is even greater, about 50% [9].

Fine needle aspiration cytology (FNAC) is the most accurate diagnostic test for differentiating benign from malignant thyroid nodules [3–5, 10, 11]. In CTN, the amount and macroscopic appearance of aspirated cystic fluid (clear, yellow, brown, or bloody) is not indicative of its benign or malignant origin [6, 7, 12, 13]. Cytological

examination of specimens arising from these nodules may show clusters of follicular cells that allow us to make a cytological diagnosis of benign or malignant nodules. But, in many cases, 20–50% of times, the smears only show cystic changes (macrophages), bloody material or cellular absence, especially when cystic component is greater [6, 7, 9, 12, 14–18]. In these cases a cytological diagnosis of unsatisfactory or nondiagnostic sample is traditionally made [2, 5]. However, some laboratories have considered as benign those nodules whose specimens only show cyst content [19, 20] so there is a matter of concern [21].

In this report we review our experience with nondiagnostic FNAC of patients with CTN who underwent surgery. We collect histopathologic diagnoses of the nodule and another possible histopathologic diagnoses outside the nodule, and we compare them between those patients whose presurgical nondiagnostic FNAC showed typical cystic changes (C-FNAC), with those patients whose presurgical nondiagnostic FNAC showed acellular specimens or only bloody content (A-FNAC).

Materials and methods

Study subjects

A retrospective review of all the patients referred for FNAC between 2003 and 2008 was conducted. The study has been approved by the local institutional review board. A total of 927 consecutive aspirations in 772 patients were examined. Selected criteria for inclusion were the patients with echographic CTN, with a nondiagnostic FNAC after two consecutive attempts, and who underwent surgery at our institution. Patients with exposure to head or neck ionizing radiation were not included. From each patient, the following information was recorded: sex, age, serum thyrotropin, echographic size and volume of the nodule, echographic uni- or multi-nodularity, and, pathologic diagnosis of the excised thyroid.

The patients were referred for surgery when nodule size was higher than 4 cm and they had cystic recurrence after needle aspiration, or if they had symptoms or signs of local compression.

Written informed consent was obtained from all the subjects.

Echographic examination

Composition of the nodule was assessed subjectively by radiologists who performed the ultrasound examination using a 6–12-MHz transducer. CTN were defined as nodules with more than 25% of cyst content [9, 22]. The volume of the nodule was calculated using the following equation: $V = \pi abc/6$ (V: volume, π: number pi, a: the largest diameter, b and c: the other two perpendicular diameters) [13]. Multinodularity was defined as echographic presence of two or more nodules bigger than 1 cm.

Fine needle aspiration cytology

We performed FNAC on an outpatient basis. All aspirations were performed by the same physician. The area to be aspirated was identified by palpation. The procedure was done with the patient in the supine position with a pillow under the neck and the head flexed backwards to expose the anterior neck. The overlying skin is cleansed with antiseptic. Local anesthesia is not applied. A 23-gauge needle on a 10 ml syringe hold in a pistol-grip is used to enter the lesion. The needle is placed into the nodule fixed by one hand. The aspirator applies suction and moves the needle back and forth within the nodule. Suction is then released and the needle is withdrawn. In each nodule, two aspirations are usually done at different sites. In CTN the fluid is evacuated as completely as possible, then placed in glass tubes and concentrated by centrifugation. Any palpable lesion that remains is reaspirated to sample solid areas. In solid nodules the aspirated material is expelled onto glass slides as small drops, and is smeared by gentle pressure with a second glass slide placed flat on the first. An average of six smears are prepared. Usually two slides are air-dried to be stained using the May-Grünwald-Giemsa technique, and four other slides are immediately wet-fixed in 96% ethyl alcohol to be stained using the Papanicolaou staining. Cystic fluid is stained using the same technique after concentration. After the procedure is completed, the patient remains under observation for a few minutes and then allowed to depart. Complications are mild temporary pain and minor local hematomas.

Rebiopsy has been performed when the initial FNAC was nondiagnostic. If this second FNAC reported the same outcome, no more biopsies were done. In patients with benign FNAC, during follow-up, a new biopsy is made only if the nodule enlarged more than 30% in one or more diameters at 6 months of echographic control.

Cytological diagnoses

Cytological diagnoses are categorized as diagnostic or satisfactory and nondiagnostic or unsatisfactory. Satisfactory samples are at least two smears which contains six or more groups of well-preserved follicular cells, each group composed of at least ten cells [2, 21, 23]. Exceptions to this numeric requirement of follicular cells where adopted from British Thyroid Association and Royal College of Physicians [23] and the recent Bethesda recommendations [21]. Any specimen that contains less than six groups of

follicular cells but abundant colloid is considered benign and not unsatisfactory. Likewise, whenever a specific diagnosis can be rendered (lymphocytic thyroiditis, etc.) and whenever there is any atypia, the specimen is considered satisfactory for evaluation.

When the samples do not fulfil the above criteria, they are considered nondiagnostic or unsatisfactory for cytological diagnosis. Nondiagnostic samples were grouped in two variants according to cellular findings seen in the smears:

- C-FNAC: smears with cellularity consistent in histiocytes, often with foamy cytoplasm or with hemosiderine granules in their cytoplasm, sometimes multinucleated, and with cholesterol crystals. Colloid is scanty or absent.
- A-FNAC: acellular smears or only bloody smears. Colloid is scanty or absent.

Histopathological analysis

Thyroid specimens were fixed with 10% neutral buffered formalin solution. After 48 h, each nodule was totally or subtotally sampled (with at least ten sections comprehensive of capsule) and embedded in paraffin. Serial slides stained with hematoxylin and eosin were examined. The presence of benign or malignant neoplasias, as well as non-neoplastic lesions were diagnosed following the established criteria.

Statistical analysis

Data analysis

Age, echographic volume of nodule, largest echographic diameter of the nodule, and serum thyrotropin, were compared between the patients grouped according to the malignancy of their thyroid nodule, and according to their group of FNAC, by Mann–Whitney U test. Sex, multinodularity, and histopathologic diagnosis were compared between the above groups by Fisher's exact test. Logistic regression analysis was performed to examine the influence of registered variables on the malignancy of the nodule, and, also on the group of FNAC. A two-sided P value less than 0.05 was considered statistically significant.

Results

Histopathologic outcomes

A total of 36 patients (45.7 ± 13 years old; 30 females) fulfilled the selected criteria and were included in the study. Histopathologic diagnoses are listed in Table 1. Four patients (11.1%) had carcinoma in their nodules. In all four cases a cystic papillary carcinoma was present: two cases of usual papillary carcinoma, and, two cases of follicular variant. Table 2 compares characteristics of the patients with or without malignancy in their nodules. The age of patients with malignant CTN tended to be lower than the age of patients with benign CTN. Nodule volume and largest diameter of the nodule were similar between these groups of patients. No differences were detected in sex, serum thyrotropin nor other diagnoses outside the nodule. Multinodularity tended to be higher and the presence of lymphocytis thyroiditis tended to be lower in the group of patients with benign CTN.

Table 1 Histopathologic diagnoses of the excised thyroid nodule

	n (%)
Nodular hyperplasia	27 (75)
Follicular adenoma	3 (8.3)
Thyroglossal cyst	2 (5.6)
Papillary carcinoma	4 (11.1)

Comparison between patients with C-FNAC and A-FNAC

According to results of FNAC performed before surgery, 21 patients had nondiagnostic FNAC but with typical cystic changes (C-FNAC) and 15 patients had nondiagnostic FNAC with acellular or with only bloody specimen (A-FNAC). Patients with C-FNAC were younger than patients with A-FNAC (41.3 ± 12.6 vs. 51.8 ± 11.2 years; $P < 0.02$). No other differences were seen with respect to sex of patients, volume of the nodules, largest diameter of the nodules, echographic multinodularity, nor serum thyrotropin (Table 3).

The histopathologic diagnoses in the 36 patients with CTN grouped according to FNAC variants are shown in Table 3. Pathologic findings in their nodules were separated from other pathologic findings found in the rest of the gland. Distribution of lesions seen in CTN is similar in both groups. Malignancy rates were slightly higher in patients with C-FNAC but without differences in the statistical analysis (14.3 vs. 6.6%). However, there were some differences in concomitant lesions seen in the gland, outside of the nodule (Table 3). Lymphocytic thyroiditis was observed in up to one-third of the patients with C-FNAC and in no patient with A-FNAC. Papillary microcarcinoma (size less than 1 cm) was found outside the nodule in two patients with C-FNAC (9.6%) and in no patient with A-FNAC.

Analysis by means of logistic regression showed that only age was independently associated to group of FNAC.

Table 2 Comparison between patients with benign and malignant complex thyroid nodules

	Benign nodule	Malignant nodule	*P* value
Number of patients	32	4	–
Age (mean ± SD)	47 ± 12.9 years	34.7 ± 7.3 years	ns
Sex	27 females (84.3%), 5 males (15.6%)	3 females (75%), 1 male (25%)	ns
Volume of nodule	23.6 ± 18.6 ml	14.7 ± 12.7 ml	ns
Largest diameter of the nodule	44.3 ± 14.6 mm	37.2 ± 8.9 mm	ns
Multinodularity	20 cases (62.5%)	1 case (25%)	ns
Serum thyrotropin (mean ± SD)	1.23 ± 0.97 mU/l	1.11 ± 0.84 mU/l	ns
Other diagnoses outside the nodule			
Lymphocytic thyroiditis	6 (18.7%)	1 (25%)	ns
Unifocal papillary microcarcinoma	1 (3.1%)	0 (0%)	ns
Multifocal papillary microcarcinoma	1 (3.1%)	0 (0%)	ns

Table 3 Characteristics of patients, complex thyroid nodules, and histopathologic findings of surgical thyroid removed, grouped according variants of FNAC

	C-FNAC (cystic changes)	A-FNAC (acellular or bloody)	*P* value
Number of patients	21 (58%)	15 (42%)	–
Age (mean ± SD)	41.3 ± 12.6 years	51.8 ± 11.2 years	<0.02
Sex	18 females (85.7%), 3 males (14.3%)	12 females (80%), 3 males (20%)	ns
Volume of nodule	21.9 ± 11.7 ml	29.1 ± 32.5 ml	ns
Largest diameter of the nodule	42.5 ± 10.7 mm	45.1 ± 18.6 mm	ns
Multinodularity	13 cases (61.9%)	8 cases (53.3%)	ns
Serum thyrotropin (mean ± SD)	1.06 ± 0.84 mU/l	1.46 ± 1.01 mU/l	ns
Histopathologic diagnoses of the nodule			
Nodular hyperplasia	15 (71.4%)	12 (80%)	ns
Follicular adenoma	2 (9.5%)	1 (6.6%)	ns
Benign thyroglossal duct	1 (4.8%)	1 (6.6%)	ns
Papillary carcinoma	3 (14.3%)	1 (6.6%)	ns
Others diagnoses outside the nodule			
Lymphocytic thyroiditis	7 (33.3%)	0 (0%)	<0.02
Unifocal papillary microcarcinoma	1 (4.8%)	0 (0%)	ns
Multicentric papillary microcarcinoma	1 (4.8%)	0 (0%)	ns

Discussion

We investigated the malignancy rate in patients with CTN whose FNAC was nondiagnostic, without history of head or neck irradiation, and who underwent surgery, finding a rate of 11.1%. In all the cases they were papillary carcinomas. Patients with malignant nodules did not show any difference in comparison to the patients with benign nodules, in respect to demographic data (age, sex), size of the nodule, presence of multinodularity, serum thyrotropin, and another histopathologic diagnoses outside the nodule. We compared those patients whose nondiagnostic FNAC showed cystic changes (C-FNAC) with another group of patients with the same type of thyroid nodules but whose nondiagnostic FNAC was acellular or showed only bloody content (A-FNAC). The rate of malignancy found in the nodule was slightly higher in patients with C-FNAC than in A-FNAC (14.3 vs. 6.6%; *P*: ns). Again, malignancy found in the gland outside the nodule, consisting of papillary microcarcinoma, was slightly higher in patients with C-FNAC than in patients with A-FNAC (9.6 vs. 0%; *P*: ns). Analysis of differences between these two groups shows that patients with C-FNAC were younger (41.3 ± 12.6 vs. 51.8 ± 11.2 years; $P < 0.02$) and more frequently had lymphocytic thyroiditis outside the nodule (33.3 vs. 0%, $P < 0.02$).

Thyroid nodules are usually benign [14, 24, 25]. However, the presence of a thyroid nodule in a patient immediately raises the question of its malignancy. This has been estimated in 5–10%, independent of how many nodules are

Table 4 Data referent to malignancy in excised thyroid nodules with nondiagnostic FNAC

References	Number cases[a]	Type of nodule	Type of goiter[b]	Rate of malignancy	Antecedent irradiation
Sarda et al. [12]	61	100% Mixed or cystic	100% SN	4.9%	NA
De los Santos et al. [7]	24	50% Cystic, 50% solid	NA	8.3%[c]	11%
McHenry et al. [17]	92	NA	100% SN	9%	10.9%
Chow et al. [31]	27	41% Solid, 53% mixed or cystic	55.6% SN, 29.6% MN	37%[d]	15%
Alexander et al. [9]	42	NA	NA	11.9%	NA
Yang et al. [19]	46	NA	NA	11.9%	NA
Present series	36	100% Mixed	41.7% SN, 58.3% MN	11.1%[e]	0%

NA not available

[a] Patients that underwent surgery with nondiagnostic result of the FNAC of the thyroid nodule

[b] *SN* Single nodule; *MN* multiple nodules

[c] 16.6% in patients with cystic nodules and 0% in patients with solid nodules

[d] 40% in SN, 25% in MN; 57% in solid nodule, 33.3% in complex or cystic nodules; four cases less than 10 mm

[e] All occurs in SN

present in the gland, and of their size (less or more than 10 mm) [3–5, 10, 22, 26, 27]. FNAC and sensitive ultrasonography are the methods used to distinguish benign from malignant nodules, and in selecting patients for surgery [5, 11, 22, 25, 26]. But FNAC has the inconvenience of nondiagnostic results. The rate of nondiagnosis for palpation-guided FNAC is 5–25% [3, 4, 10, 15, 17, 19, 25, 28–32]. Although the rate of nondiagnostic FNAC is reduced to a 3–16% when ultrasound-guided FNAC is performed [9, 15, 27, 30, 31], it still remains elevated. Ultrasound-guided reaspiration of nodules with an initial nondiagnostic FNAC has a slightly better rate of diagnostic smears than reaspiration without ultrasound guidance (66 vs. 56%) [32]. One of the main reasons for nondiagnostic specimens is the inclusion of aspirates arising from cysts [6, 7, 9, 12, 15–18]. To improve outcomes of FNAC in CTN, the last Consensus Conference Statement of the American Society of Radiologists in Ultrasound recommended that mixed solid and cystic or almost entirely cystic with solid mural component thyroid nodules should undergo FNAC if the maximum diameter is $\geq$2 cm [22].

In the past, CTN were regarded as a benign finding, but in the last years it has been widely recognized that these lesions have the same rate of malignancy as solid nodules [6, 7, 12, 18, 33]. The cystic component of CTN primarily represent benign degenerated colloid nodules except for some papillary thyroid cystic cancers [3, 5, 6, 8, 13, 27, 34], and other rare cystic carcinomas [6, 7, 18, 33]. When an acellular or bloody fluid is obtained from a CTN by FNAC, the sample is considered unsatisfactory for cytological diagnosis or nondiagnostic FNAC [2, 5]. If cellularity is made up of degenerative foam cells (macrophages only), the sample may be considered unsatisfactory for cytological diagnosis because the parenchyma of the nodule has not been sampled, and one cannot exclude a cystic papillary carcinoma [2, 5]. Otherwise this nodule may be considered as a benign lesion by some laboratories [19, 20] that consider negligible the risk of a false-negative result [21, 35]. Thus, management of patients whose FNAC of a CTN is unsatisfactory for cytological diagnosis is usually based on clinical data, and patients are closely monitored or managed surgically, according to clinical judgment [26, 36]. We would know if the specific relation between variants of nondiagnostic cytology of CTN and histopathologic outcomes after surgical treatment, may be helpful in this environment.

Given the frequency of nondiagnostic aspirations, an estimate of the likelihood of malignancy is desirable in these patients. In the selected group of patients who are referred for surgery, the malignancy yield ranges from 4.9 to 37%, depending on patient selection [7, 9, 12, 17, 19, 32] (Table 4). Therefore, selection of the patients with a high suspicion of malignancy to be treated surgically results in a highest rate of malignancy. We have found 11.1% of malignancy in 36 patients undergoing surgery for CTN with nondiagnostic FNAC. Our patients had no history of head or neck radiation, so their risk of malignancy might have been less than others. They were not included in the study because they are currently undergoing surgery due to their high risk of malignancy [1, 17, 28]. Age and sex of our patients, volume of the nodule, largest diameter of the nodule, serum thyrotropin, and other diagnoses outside the nodule were similar between those with benign and those with malignant nodules.

In our study, a slightly higher prevalence of malignant nodules (14.3 vs. 6.6%; *P*: ns) and microcarcinoma outside the nodule (9.6 vs. 0%; *P*: ns) was seen in the group of patients with C-FNAC compared with patients with A-FNAC. Furthermore, a higher prevalence of lymphocytic thyroiditis (33.3 vs. 0%; $P < 0.02$) was seen in our group of

patients with C-FNAC. There are some evidences that may explain these relations. In respect to the association of cytic changes in CTN and lymphocytic thyroiditis, the necrosis of a solid nodule and cystic formation may be seen as an imbalance between growth and the precisely regulated process of angiogenesis. Different mechanisms in this pathogenesis have been suggested, as high concentration of vascular endothelial growth factor in cystic fluid, that may stimulate vascular permeability and promote accumulation of fluid [37]. In some cases a high titer of antithyroid antibodies has been found in cystic fluid, suggesting that autoimmunity might participate in the formation of cyst [38]. Cysts also have been considered as the end result of apoptosis induced by Hashimoto thyroiditis [39, 40]. On the other hand, with respect to the association between thyroid carcinoma and lymphocytic thyroiditis, a recent article reviews the occurrence of incidental papillary carcinoma in thyroid glands removed for benign disease, and suggests that the association of incidental papillary carcinoma with Hashimoto's thyroiditis may indicate a link to thyroid cancer [41]. Fiore et al. [42] have found that frequency and severity of lymphocytic infiltration in histological samples of 688 patients was significantly higher in 304 patients with papillary thyroid cancer (affected 82–85% according to the patients with multinodular goiter or single thyroid nodule) than in 384 patients with benign thyroid nodular diseases (affected 45–71% according to the patients with multinodular goiter or single thyroid nodule). Boi et al. [43] had seen indirect evidence supporting a significant association between papillary thyroid carcinoma and thyroid autoimmunity. They found 13.7% of thyroid carcinoma in nodules of patients with positive serum thyroid autoantibodies, and 8.4% in patients with negative serum thyroid autoantibodies. Some years before, Ott et al. [44] reported that incidence of thyroid carcinoma in patients with solitary cold nodules and Hashimoto's thyroiditis was as higher as 31.5% in patients without radiation exposure.

The patients with C-FNAC were younger than the patients with A-FNAC. Demographic features of 769 patients with Hashimoto's thyroiditis show a mean age of 41.76 ± 12.49 years, similar to the patients with C-FNAC [45]. In addition, in 302 patients with differentiated thyroid carcinoma (62% papillary thyroid carcinoma), Bhargav et al. [46] found that the mean age of the patients was 42 ± 14 years. Younger age in our patients with C-FNAC compared to patients with A-FNAC, may be in relation to higher prevalence of lymphocytic thyroiditis and papillary carcinoma. Despite the fact that the number of patients is low, the age of patients with A-FNAC is similar to the age of patients undergoing surgery because of benign multinodular goiter. In a recent study [47], 883 patients with benign multinodular goiter underwent thyroid surgery; the mean age was 51 ± 1 years.

The goal in evaluating a thyroid nodule is to properly identify and surgically excise the few malignant nodules while avoiding surgery in patients with benign nodules. CTN are a common clinical entity that represents a major challenge for cytological diagnosis due to a particularly high frequency of nondiagnostic specimens. In order to improve the adequacy of the specimens obtained from FNAC, Redman et al. [15] have suggested that ultrasonographically guided FNAC with onsite evaluation of cytology specimens substantially reduces the inadequacy of cytology specimens, from 7 to 3% in their series. Capelli et al. [18] have reduced the rate of inadequate specimens from 15.5 to 5.2% by adopting stylet needles to perform FNAC in CTN. In our study, the analysis of variants of nondiagnostic cytology, differentiating between specimens with typical cystic changes and specimens with acellular or only bloody content, shows that the rate of malignancy is similar between these two groups, so we need to continue searching for any finding or technical modification that may help to establish more accurately the difference between benign and malignant nodules.

In conclusion, we reported a 11.1% malignancy rate in CTN with nondiagnostic FNAC of patients that underwent surgery. Analysis of the cytologic variants of nondiagnostic FNAC in these CTN, showed that C-FNAC had a slightly higher rate of malignancy than A-FNAC (14.3 vs. 6.6%; *P*: ns). This weak relationship may be mediated by the younger age ($P < 0.02$) and higher prevalence of lymphocytic thyroiditis ($P < 0.02$) in the group of patients with C-FNAC, in considering the previously reported associations between age, thyroid carcinoma, and lymphocytic thyroiditis.

We acknowledge potential concerns related to our study methods that should be kept in mind. First, the study has the limitations of a retrospective study. Second, patients submitted for surgery were not selected randomly, allowing for potential physician or patient preferences. Finally, our sample size is relatively small, so others studies are needed to confirm our results.

Conflict of interest and financial disclosure The authors have nothing to declare.

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