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Value of Fine Needle Aspiration Biopsy in Toxic Thyroid Adenoma

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ABSTRACT:

Background: The co-existence of thyroid cancer (TC) and hyperthyroidism (HT) cause serious diagnostic, therapeutic and prognostic difficulties Fine-needle aspiration biopsy (FNAB) is considered as essential step in the checkup of the thyroid nodule. **Aim of the work**. Assessment of the clinical value of FNAB and to determine frequency of thyroid cancer in patients with autonomous toxic thyroid adenoma, before radioactive iodine therapy. **Methodology:** All patients underwent clinical examination, thyroid hormonal profile analysis, neck ultrasound, Tc-99 thyroid scan and Fine Needle Aspiration Biopsy (FNAB). Twelve Patients with positive, suspicious or non-diagnostic FNAB results underwent thyroidectomy and histopathological analysis. **Results:** This study included forty one patients, 23 females (56.1%) and 18 males (43.9%) with mean age 39.8 (±9.3) years. All patients have elevated T3, T4 and suppressed TSH. All patients underwent FNAB; 29 patients (70.7%) were negative, two patients (4.9%) had TC, one patient (2.4%) was suspicious and 9 patients (22%) were non-diagnostic. Twelve patients with positive, suspicious or non-diagnostic FNAB results underwent thyroidecetomy followed by histopathological examination of the surgical specimens that confirmed features of TC in two patients with positive FNAB and one patient with suspicious FNAB, in addition to another one patient with non-diagnostic FNAB. Thyroid cancer was found on 4 patients (9.76%), three patients had papillary thyroid cancer and the fourth had follicular form proved by surgery.

Conclusion: Addition of FNAB to work up list of patients with autonomous toxic thyroid adenoma prior to radioactive iodine therapy has added value in detection of malignancy. However surgery is recommended to confirm or exclude malignancy in patients with suspicious or non-diagnostic FNAB results.

Keywords; Autonomous toxic adenoma; thyroid cancer; fine needle aspiration biopsy**.**

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INTRODUCTION:

Thyroid cancer (TC) is one of the commonly frequent endocrine malignancies [(1)]. It represents about 1% of global malignancies [(2)]. Hyperthyroidism (HT) is defined as a state of over synthesis and excretion of thyroid hormones [(3)]. There are many forms of hyperthyroidism such as Graves' disease, toxic adenoma and Plummer's disease (toxic multi-nodular goiter) [(1)]. Autonomous toxic adenoma is characterized on thyroid scan by increased active uptake with partial or complete suppression in the surrounding thyroid tissue in patient with manifest hyperthyroid signs [(4)]. The co-existence of TC and HT is unusual; the coexistence of TC and HT causes diagnostic, therapeutic and prognostic difficulties [(5)]. The malignant thyroid nodules do not concentrate radionuclides and appear as "cold" areas in thyroid scan. However, malignancy may be found in functioning thyroid nodules, the main issue is to differentiate the malignant nodules requiring surgery from the benign ones that can be treated by radioactive iodine [(6)]. Fine-needle aspiration biopsy (FNAB) is procedure that is usually done on an outpatient basis. It is considered as essential step in the checkup of the thyroid nodule; it used on wide scale, well tolerated and has low risk of complications. It also helps in the decision making for surgical resection of the thyroid gland [(7,8)]. No standard means of reporting FNAB cytology specimens. The report may be read as benign, malignant, indeterminate, or non-diagnostic [(9)]. Among patients with toxic adenomas, radioiodine treatment not only alleviates hyperthyroidism but also decreases the adenomas size [(10)]. **Aim of the work:** Our target was to assess the clinical significance of FNAB for detection of thyroid cancer in patients with autonomous toxic thyroid adenoma before radioactive iodine therapy and to determine frequency of thyroid cancer in those patients.

PATIENTS AND METHODS:

This backdated study involved 41 patients with autonomous toxic adenoma seen at Nuclear Medicine Units of both Zagazig University and Al-maadi Military Hospitals throughout the period of January 2016 till December 2017.

Selection criteria: Patients with different sex, more than 18 years old and had autonomous toxic thyroid adenoma diagnosed by thyroid scan (see below). The diagnosis of nodule autonomy required the documentation of both Tc99m pertechnetate uptake into the nodule and suppressed uptake in the normal thyroid parenchyma on scintigraphy performed during hypo-thyrotropinemia (low TSH).

Exclusion criteria: Patients with the following criteria are excluded from the study: Age less than 18 years old, history of neck irradiation in childhood, other causes of hyperthyroidism, non-toxic autonomous adenoma and also patients with cold nodule (s) either at the adenoma itself or at the rest of the thyroid gland. Pregnant and lactating ladies are not included in this study.

Clinical evaluation: history (including age, sex, complaint, illness duration, history of anti-thyroid drugs and surgery) and general examination. Local neck examination was also done to evaluate the thyroid gland (size, consistency, nodularity) and exclude other neck swellings.

Laboratory investigations: Serum TSH level, FT3, FT4 were done (Normal range: TSH: 0.5- 5 mIU/L, T3: 60- 181 ng/mL, T4: 5.5- 12.3 ng/ml. They were measured by Immunoassay Test.

Thyroid Scintigraphy: Thyroid scan was performed for all patients using free technetium-99m pertechnetate (Tc 99m). The administrated dose was 5.0 mCi of Tc-99m pertechnetate and injected via intravenous route (I.V).

Anterior neck imaging was acquired in a supine position with extended neck and the gamma camera fitted with low energy high resolution parallel-hole collimator, with window width 15% and window level 140 Kev in a 128x128 matrix for 500,000 counts per view. Quantitative evaluation of thyroid uptake was estimated using computer software. Normal reference range for thyroid uptake with Tc 99m = (0.5-4%).

Qualitative image evaluation for thyroid tracer distribution, presence of nodules (cold, worm or hot), background and salivary glands activity and also retrosternal extension was also considered.

Neck U/S and Doppler study: for evaluation of thyroid gland size, consistency, echo pattern, gland vascularity, presence of calcification, presence and other thyroid gland nodules as well as assessment of cervical lymph nodes.

Surgical Intervention: Twelve patients, who had positive, suspicious and non-diagnostic FNAB results, underwent near total thyroidectomy, followed by histopathological examination of the resected thyroid gland.

Histopathological examination: FNAB was done for all patients under sonar guided with aseptic precautions by using a 10 cm^3 syringes and 23-24 gauge needles. Smears were air dried and stained with H&E stain. The obtained biopsies either FNAB and/or surgical specimens were examined and reviewed by an expert pathologist. The results of FNAB were recorded as negative, positive, suspicious and non-diagnostic. The suspicious result was considered positive till proved otherwise.

We divided our patients according to the results of FNAB into two groups:

1- Non-risky group which included 29 patients (70.7%) with negative FNAB.

2- Risky group which included 12 patients (29.3%) with positive, suspicious and non-diagnostic results of FNAB.

Statistical analysis: The collected Data coded, entered and analyzed using Microsoft Excel software and imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data represented as number and percentage, quantitative continues group represented by mean ± SD, the following tests were used to test differences for significance difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups were done using t test or Mann Whitney, multiple by ANOVA or Kruskal Wallis, correlation by Pearson's correlation or Spearman's. P-value less than 0.05 was considered statistically significant and P value less than 0.001 for high significant result.

RESULTS:

This study included 41 patients with autonomous toxic thyroid adenoma, 23 (56.1%) females and 18 (43.9%) males with mean age 39.8 (±9.3) years. FT3 and FT4 were elevated for all patients with mean values (225.4 ± 44.4 ng/mL and 14.4 ± 2.19 ng/mL, respectively). TSH was suppressed with mean value 0.14 ± 0.16 mU/L. Manifest thyrotoxic symptoms were recorded in 35 (85.4%) patients. Only 26 (63.4%) patients received anti-thyroid therapy. The mean size of autonomous toxic thyroid adenoma measured by ultrasound was 3.6 ± 1.3 cm. Twenty four patients (58.5%) had thyroid adenoma at the right thyroid lobe and 17 patients (41.5%) had adenoma at the left thyroid lobe. The most common ultrasound feature was hyper-vascular pattern as it was seen in 85.4% of patients (35/41). There was higher frequency of adenomas with homogenous echo-pattern 70.7% (29/41) than adenomas with heterogeneous echo pattern 29.3% (12/41).Micro calcification was not uncommon as 8/41 patients (19.5%) had sonographic evidence of micro-calcification but only one patient had abnormal lymph node. On thyroid scan also, the homogenous pattern was more frequent 70.7% (29/41) than the heterogeneous pattern 29.3% (12/41) and both have high mean value of thyroid uptake (9.8 ± 6.5). All patients underwent FNAB. The analysis of fine needle aspiration biopsies (FNAB) indicated that 29 patients (70.7%) were negative, two patients (4.9%) had TC, one patient (2.4%) was suspicious for TC and 9 patients (22%) were non-Diagnostic. Twelve patients (29.3%) with positive, suspicious and non-diagnostic FNAB underwent thyroidectomy, the histopathological analysis of their surgical specimens showed that 8 patients were negative for TC, while 4 patients confirmed to be positive for TC (two patients with positive FNAB, one patient with suspicious FNAB and one patient with non-diagnostic FNAB). ***(Table 1) and Figure (1, 2)***.

Table 1: Characteristic of Patients with Autonomous Toxic Thyroid Adenoma.

			No	(%)	Mean ± SD
Clinical Data	**Age (year)**	------	**---**	**----**	**39.8 ±9.3**
	Sex	Male	**18**	**43.9**	**------**
		Female	**23**	**56.1**	**------**
	Thyro-toxic Symptoms	Yes	**35**	**85.4**	**------**
		No	**6**	**14.6**	**------**
	Ant thyroid Therapy.	Yes	**26**	**63.4**	**------**
		No	**15**	**36.6**	**------**
Laboratory Data	**TSH level**	------	**---**	**----**	**0.14 ± 0.16**
	T3 level	------	**---**	**----**	**225.4± 44.4**
	T4 Level	------	**---**	**----**	**14.4 ± 2.19**
Ultrasound Data	**Nodule Site**	Right	**24**	**58.5**	**------**
		Left	**17**	**41.5**	**-------**
	Nodule Size (cm)	------	**---**	**----**	**3.6 ± 1.3**
	US pattern	Homogn.	**29**	**70.7**	**-------**
		Hetero.	**12**	**29.3**	**-------**
	Calcific Spots	Yes	**8**	**19.5**	**-------**
		No	**33**	**80.5**	**--------**
	Doppler US	Normal	**6**	**14.6**	**------**
		Hyper.	**35**	**85.4**	**------**
	US LNs	Normal	**40**	**97.6**	**------**
		Abnormal	**1**	**2.4**	**------**
Thyroid scan Data	**Adenoma Shape**	Rounded	**18**	**43.9**	**------**
		Oval	**23**	**56.1**	**------**
	Scan pattern	Homo.	**29**	**70.7**	**------**
		Hetero.	**12**	**29.3**	**------**
	Thyroid uptake	------	**---**	**----**	**9.8 ± 6.5**
Biopsy and Surgical Data	**Biopsy type**	FNB only	**29**	**70.7**	**------**
		FNB & Surg.	**12**	**29.3**	**------**
	Thyroidectomy	Yes	**12**	**29.3**	**------**
		No	**29**	**70.7**	**------**

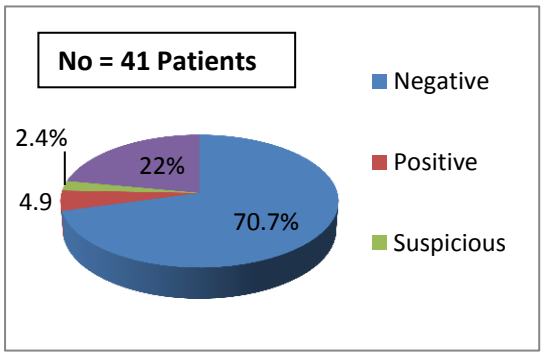

Figure 1: Results of FNAB.

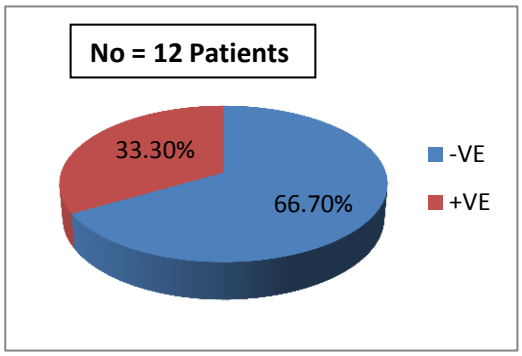

Figure 2: Results of Surgical Specimens.

Table 2: Comparison between Histopathological Results of FNAB in relation to Pathological Results of Surgical Specimens.

		Results of surgical specimens			
FNB Result	**Total**	**+VE**	**-VE**	**X^2**	**P**
	12 (100%)	**4 (33.3%)**	**8 (66.7%)**		
Positive	2 (16.7%)	2 (100%)	0 (0.0%)		
Suspicions	1 (8.3%)	1 (100%)	0 (0.0%)	8.1	0.018*
Non Diagnostic	9 (75%)	1 (11.1%)	8 (88.9%)		

The mean values of the age, nodule size, TSH level and thyroid uptake are comparable between both groups. The frequency of the heterogeneous echo pattern, hypo-echogenicity and hyper vascular Doppler between Non-risky (n=29) and risky patients (n=12) were 7 (24.1%), 2 (6.9%) and 24 (82.3%) versus 5 (41.7%), 1 (8.3%) and 11 (91.6%) respectively. One patient of the risky group with hypo-echogenicity proved to have papillary thyroid cancer on both FNAB and surgical biopsies. Also one patient of this group showed hyper vascular pattern with central flow. Micro-calcifications were found in 4 patients at each group, two patients (50%) of the risky group were positive for cancer ***Figure (3)***.

Table 3: Comparison between Risky and Non-Risky Patients focusing on Clinico-Pathological Factors.

		* Non Risky Patients (N=29)		* Risky patients (N=12)		t	p
		No (%)	Mean ± SD	No (%)	Mean ± SD		
Age (year)	------	29 (%)	40.1 ±9.7	12 (%)	39.08±8.6	-0.328	0.475
Sex	Male	13 (44.8%)	--------	5 (41.7%)	--------	0.034	0.85
	Female	16 (55.2%)	--------	7 (58.3%)	--------		
TSH level	------	--------	0.16 ± 0.15	--------	0.14± 0.17	0.400	0.691
Nodule Site	Right	16 (55.2%)	--------	8 (66.7%)	--------	0.46	0.49
	Left	13 (44.8%)	--------	4 (33.3%)	--------		
Nodule Size (cm)	------	--------	3.6 ± 1.3	--------	3.4± 1.1	-0.463	0.646
US pattern	Homo.	22 (75.9%)	--------	7 (58.3%)	---------	1.26	0.26
	Hetero.	7 (24.1%)	--------	5 (41.7%)	---------		
Calcific Spots	Yes	4 (13.8%)	--------	4 (33.3%)	---------	2.06	0.15
	No	25 (86.2%)	---------	8 (66.7%)	---------		
Echogenicity	Hyper	23 (79.3%)	---------	8 (66.7%)	---------	2.66	0.26
	Hypo.	2 (6.9%)	---------	1 (8.3%)	---------		
	Iso	4 (13.8%)	---------	3 (25%)	---------		
US LNs	Normal	29 (100%)	-------	11 (91.6%)	-------	3.19	0.203
	Abnormal	0 (0.0%)	--------	1 (8.4%)	--------		
Doppler US	Normal	5 (17.2%)	-------	1 (8.4%)	-------	3.19	0.203
	Hypvasc.	24 (82.3%)	--------	11 (91.6%)	--------		
Thyroid uptake	------	--------	9.1 ± 6.0	--------	11.6 ± 7.6	----	-----

*Non-Risky = patients with negative FNAB result
*Risky patients = patients with positive, suspicious or non-diagnostic FNAB results

As regarding the ultrasound pattern of the cervical lymph nodes, only one patient belong to the risky group has abnormal lymph node pattern on ultrasound, suggestive of infiltrative process and proved to be metastatic on histo-pathological analysis of the surgical specimens. All parameters of the table didn't show any statistically significant difference between both groups (p value > 0.05) ***(Table 3)*** and ***Figure (4)***. The frequency of thyroid cancer among the total number of study sample was 4/41 patients (9.76%). Three patients had papillary thyroid cancer and the fourth had follicular form, two patients (50%) had capsular infiltration. Vascular infiltration was found in one patient and lymph node metastases in another one ***(Table 4)***.

Table 4: Pathological features of Patients with Thyroid Cancer.

		Total No = 4	
		No (%)	**Mean ± SD**
Age (year)	----	------	36.8 ± 4.9
Nodule Size (cm)	----	------	3.95 ± 0.98
Tumor size (mm)	----	------	13.5 ± 6.4
Tumor Type	Papillary.	3 (75%)	------
	Follicular.	1 (25%)	-------
Positive LNs	Yes	1 (25%)	-------
	No	3 (75%)	-------
Capsular infiltration.	Yes	2 (50%)	-------
	No	2 (50%)	-------
Vascular infiltration.	Yes	1 (25%)	-------
	No	3 (75%)	------
Distant metastases.	Yes	0 (0%)	-------
	No	4 (100%)	------

DISCUSSION:

Thyroid nodules are frequently-encountered entities in clinical practice, occurring with a prevalence of 4% by palpation and 33% to 68% by ultrasound examination. Autonomous nodules may account for 5-10% of palpable nodules [(11)]. Nodular thyroid disease as well as functioning thyroid nodules incidence is increased in iodine deficient areas. Malignancy, however, in hot nodules is rare. However, there is a chance of cancer in autonomous nodules [(12)]. In patients with hyperthyroidism many authors described thyroid malignant neoplasms, but in most cases, they are incidentally found (out of the index nodule) [(13)]. Serum TSH is an effective tool in the diagnosis of toxic adenoma as some patients may have euthyroid state; however normal TSH level dose not exclude autonomous functioning thyroid nodule (AFTN) as stated by **Chami et al** [(14)]. In the current study all patients had suppressed base line TSH that is in agreement with **Blum et al** and **Langer et al** who found elevation of free T3 and free T4 with suppression of TSH levels in patients with solitary toxic thyroid adenoma [(15, 16)]. For thyroid nodules ultrasonography is the imaging modality of choice. Sonographic features help in characterization and suspicion of malignancy in thyroid nodules. These features include solid appearance, hypo-echogenicity, increased central vascularity, micro-calcifications, irregular margins, and the absence of a halo.

It is also helpful in choosing the site within a nodule for FNAB to improve diagnostic yield [17]. The ultrasound alone cannot reliably distinguish malignant and benign lesions [18]. As regarding the sonographic features of four patients with thyroid cancer, we found 2/4 patients (50%) with calcific spots, while hypo echogenicity, central hyper vascularity and abnormal lymph node pattern were seen in one patient each.

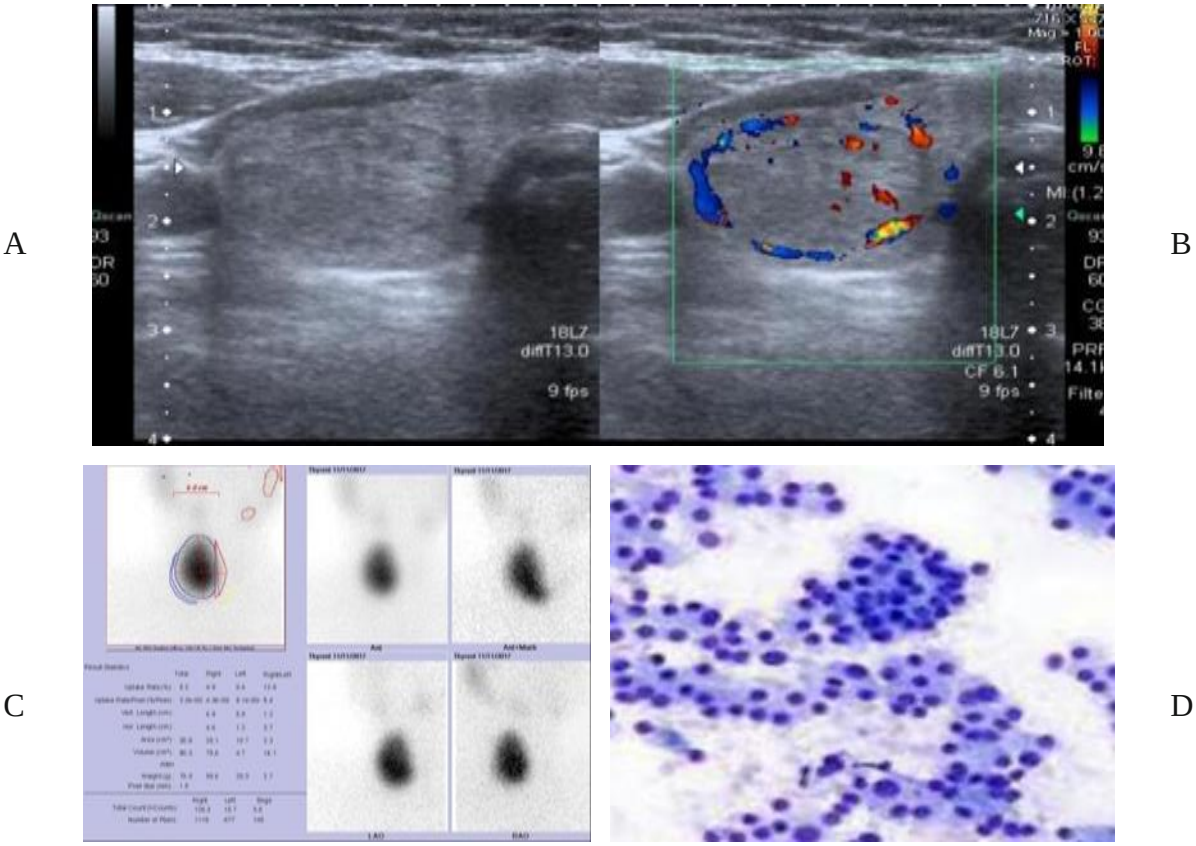

Fig 3. Fifty three 53 years old female, **A**; US image showed well-defined iso-echoic right lobe solid nodule. **B;** Doppler image displayed peripheral &central vascularity. **C:** Thyroid scan image, oval shaped intense adenoma with suppression to rest of the gland & uptake = 5.2%. **D;** Cytological findings of FNAB demonstrating, follicular adenoma with mature follicular cells and bland looking nuclei.

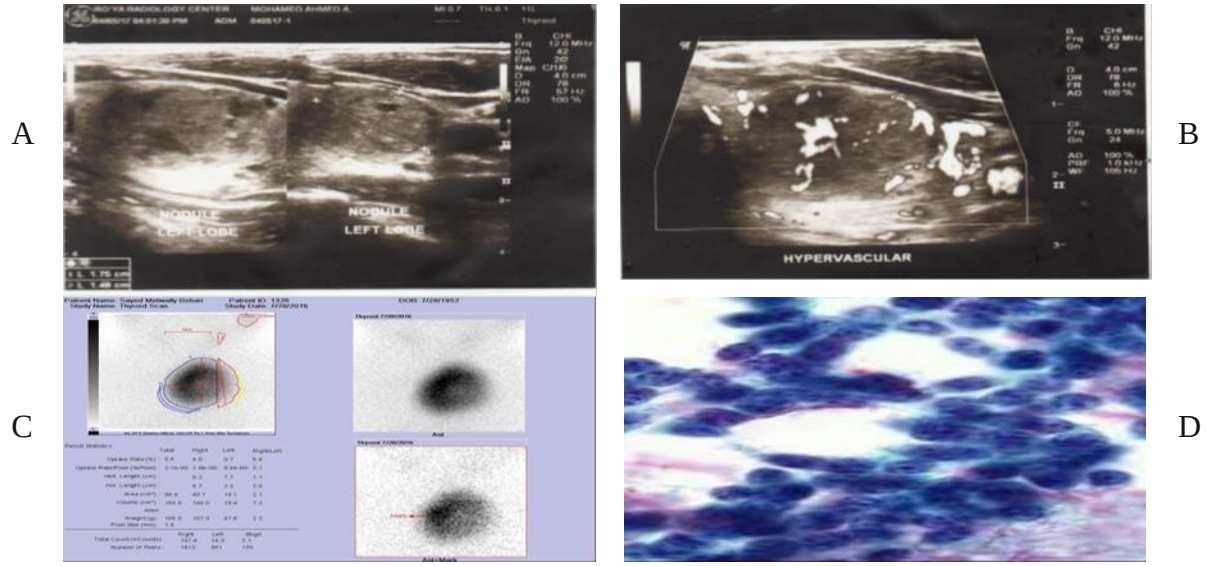

Fig 4. Forty three years old male, **A;** US image displayed well defined slightly echogenic solid left lobe nodule with areas of breaking down, **B;** Doppler image showed central and peripheral vascularity. **C;** thyroid scan image portrayed left lobe adenoma with heterogeneous uptake, suppression to the other lobe and uptake = 6.5%. **D;** FNAB revealed papillary thyroid carcinoma, with cellular aggregates of follicular cells with intra-nuclear inclusions and many nuclear inclusions , some of them are optically clear nuclei .

FNAB of thyroid nodules is minimally invasive and safe it is usually performed on an outpatient basis [(19)]. FNA is the most accurate and cost-effective tool for evaluation of thyroid nodules. It is a valuable aid in establishing the need for thyroid surgery and diagnosis and for treatment of malignancies [(20)]. In our research, three of the four patients proved to have TC had definite features of malignancy on FNAB with overall sensitivity 75%. This is consistent with **Seningen et al 2012** who stated that the sensitivity and specificity of FNAB ranged from 76%–98% and 71%–100% respectively [(21)]. In another report, based on a review of 12 studies, the median sensitivity and specificity of FNAB were 88% and 90.5% [(22)]**.** FNAB has a reported diagnostic sensitivity of 89 to 98% and a specificity of 92% for thyroid nodules. A wide malignancy range (from 2% to 37%) was reported for patients with non-diagnostic cytological features [(23)]. In the current study out of nine patients with non-diagnostic FNAB results, there was one positive case (11.1%) on surgical pathological examination. Comparable results were also reported by **Rıfkı et al** and **Anderson et al** they showed **malignancy** rate of 10.2% and 5.3% respectively for patients with non-

diagnostic FNAB [24, 25]. We reported 9.76% frequency rate of TC (4/41 patients), which is high relative incidence due to small size sample with only 2 patients proved by FNAC (4.9 %) and 4 patients detected by surgery. However, **Mizukami et al,** found thyroid cancer in 12% of cases with autonomous functioning nodules [26]. **Harach et al** also found 6/73 malignant cases (8.2%) in their study published in 2002 [27]. Among 14 case series, **Mirfakhraee et al** found that the rates of intra-nodular thyroid carcinoma resected solitary hyperfunctioning thyroid nodules ranged from 0 – 12.5% [28]. On the other hand, lower rates were reported by **Smith et al** who found malignancy rates about 7.3% and 4.5% for the patients with functioning thyroid nodules and those with single toxic nodule respectively [29]. Similar malignancy frequency (4.7%) was found by **Gabriele et al 2003** in patients with hot thyroid nodule [30]. Others reported that a functioning, or "hot," thyroid nodule is seldom malignant, with only a few reported cases of such malignancy and incidence rate 1.4% [31]. **Cooper et al 2009** reported that patients with hyper functioning nodules rarely harbor malignancy and there is no need for FNAB in this circumstance [32]. **Borges and colleagues** have shown that hyperfunctioning hot nodules have very rare potential for malignancy, thus they are seldom biopsied after scintigraphy [5]. **Erdoğan et al,** also reported a rare incidence of malignancy in hot functioning nodules [6]. **Mazzaferri** proved that the incidence of thyroid cancer in a hot functioning thyroid nodule is very low [33]**.** Also thyroid carcinomas has been described in a literature done by **Mirfakhraee et al, 2013** [34] for review of surgical case series with solitary hyper-functioning thyroid nodules treated by thyroid resection, showed an estimated variable prevalence rate of malignancy ranged from 1.4% **Cappelli et al, 2006** [31] to 23**% (Giles et al, 2008)** [35].

CONCLUSION:

The hyper functioning state of autonomous toxic thyroid adenoma does not totally exclude the possibility of malignancy, so addition of FNAB in patients with autonomous toxic thyroid adenoma prior to radioactive iodine therapy may have added value in detection of malignancy and achieves better outcomes. Finally, we recommend further large scale studies to clearly identify the value of FNAB for patients with autonomous toxic thyroid adenoma and if surgical excision should be done to confirm or exclude malignancy in patients with suspicious or non-diagnostic FNAB results.

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