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Prevalence of thyroid nodules in a sample of Egyptian systemic lupus erythematosus patients

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Abstract

Thyroid nodules (TNs) are distinct lesions inside the thyroid that can be determined from the adjacent thyroid parenchyma on ultrasonography. Complement activation, autoantibody generation, persistent inflammation, and immune-complex deposition are the hallmarks of systemic lupus erythematosus (SLE), a complicated systemic autoimmune condition that damages tissues and organs. The current study aimed to detect TNs prevalence in SLE patients, and possible malignancy in a sample of Egyptian population. This cross-sectional study included 80 cases diagnosed with systemic lupus erythematosus, attending the Endocrinology and Rheumatology outpatient clinics at Ain-Shams University Hospital, to detect the prevalence of TNs in a sample of Egyptian SLE cases. There was a positive relation between Systemic Lupus Erythematosus Disease Activity Index (SELDAI) score and TNs, also positive relation between SELDAI score and prevalence of malignancy. There was a higher remarkable number, 13 patients (43.3%), of TNs cases among the group with abnormal thyroid functions. In conclusion, the percent of thyroid malignancy among patients with SLE is the same as in general population, so that SLE itself did not increase the risk of thyroid malignancy. Also, the percent of TNs among cases with SLE was the same as in the general population. Activity of SLE in terms of SLEDAI score has relation with TNs and malignancy. Cases with SLE and TNs are more susceptible to thyroid dysfunctions.

Keywords: TNs, SLE, Systemic Lupus Erythematosus Disease Activity Index.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition marked by multisystem inflammation and autoantibodies formation. Despite that the particular etiology of SLE is unknown, several factors are related with its progression, comprising epigenetic, genetic, hormonal, immunoregulatory, ethnic, and environmental factors.[1]

Thyroid nodules (TNs) are distinct thyroid lesions that are radiologically different from the neighboring parenchyma, and their occurrence varies based on the diagnostic approach utilized and the research population.[2] TNs are the most common disorder of thyroid gland. In Egypt,

nodular goiter occurs in 4% - 7% of the population [3]. They are identified by physical assessment in 2%-6% of patients; ultrasound finds them in 19%-35% of cases, and autopsy in 8%-65% of cases. They are substantially related to female sex, iodine shortage, past radiation exposure, and old age.[4]

The clinical significance of detecting TNs is the necessity to rule out malignancy, which has been documented in up to 5% of cases, even those with nonpalpable TNs.[5] Ultrasound employing thyroid imaging reporting and data systems (TI-RADS scoring) not only recognizes the existence, size, number, malignancy, and position of TNs, but it additionally enables a physical assessment to identify previously undetected TNs, increasing the likelihood of early identification of malignant tumors. In general, in the absence of worrying signs, only TNs beyond 1 cm requires additional investigation.[2]

The American College of Radiology (ACR) proposed the ACR TI-RADS reporting method for TNs detected by ultrasound. Ultrasound observations are scored according to five criteria. The higher the cumulative score, the higher the TR (TI-RADS) level and the risk of malignancy.[6]

Fine needle aspiration (FNA) is critical in the assessment of TNs. However, investigations have indicated that nearly 30% of thyroid FNA was once labeled as "atypical", "indeterminate", and "suspicious for malignancy".[7] The Bethesda system for reporting thyroid cytopathology was created to promote consistency in identifying thyroid FNA cases and directing clinical treatment.[8]

Adult-onset SLE is correlated with a significant thyroid carcinoma (TC) prevalence.[9] Although a multi-site multinational SLE cohort research has yielded various findings.[10] Current investigations documented that malignancies prevalence in SLE differs greatly, hence a reliable and weighted analysis of the standardized incidence rate is important,[9] The present work aimed to detect TNS prevalence and possible malignancy in a sample of Egyptian population with SLE.

Subjects and Methods

Patients:

This cross-sectional study included 80 cases diagnosed with SLE, attending the Endocrinology and Rheumatology outpatient clinics at Ain-Shams University Hospital during 2023-2024, to detect the prevalence of TNs and incidence of thyroid malignancy among those patients in a sample of Egyptian SLE cases.

This study included SLE-diagnosed adult cases according to the European Alliance of Associations for Rheumatology and ACR (EULAR/ ACR 2019) classification criteria.[11]

Any patient with the following features was excluded. These included patients with chronic liver disease, pregnancy, patients with known malignancy, and family history of thyroid malignancy.

Methods

All patients of the studied groups were subjected to: complete history taking of clinical importance, complete general and cardiac examination, and laboratory assessment (thyroid profile (TSH, FT4, FT3), complete blood count (CBC), C-reactive protein (CRP), C3 and C4, thyroid perioxidase antibody which were assessed according to standard methods of the University Hospital. Thyroid ultrasound was performed by Thyroid Imaging Reporting and Data System (TI-RAD) scoring, fine needle aspiration **(**FNA) cytology of suspicious nodules regarding the TI-RAD scoring. Patients diagnosed with malignancy by **f**ine needle aspiration cytology (FNAC) were referred to the surgery.

Thyroid ultrasound (US) with TI-RADS scoring

The thyroid US with TI-RADS classification and scoring was performed according to Tessler et al., 2017,[6] as TR1: 0 points (Benign, no FNA), TR2: 2 points (Not suspicious, no FNA), TR3: 3 points (Mildly suspicious, ≥1.5 cm follow up, ≥2.5 cm FNA follow up: 1, 3 and 5 years), TR4: 4-6 points (Moderately suspicious, ≥1.0 cm follow up, ≥1.5 cm FNA follow up: 1, 2, 3 and 5 years), and TR5: ≥7 points (Highly suspicious, ≥0.5 cm follow up, ≥1.0 cm FNA, and follow up to 5 years

with 1 per year). Regarding the risk of malignancy, it was presented as TR1: 0.3%, TR2: 1.5%, TR3: 4.8%, TR4: 9.1%, and TR5: 35%.

FNA and biopsy according to TI-RADS scoring

Various endocrine surgeons conducted the FNAs using US and without conducting an on-site pathologic assessment. The cases were placed on the examination table in a semi-Fowler position, with the neck extended and the head and torso raised 30 degrees. After the TNSs were identified on ultrasound and the cases agreed to FNA, a 10-mm syringe with a 22-gauge needle was utilized to biopsy the TNSs with US assistance and suction employing a pistol. For each pass, the needle was inserted around ten times, and pressure was put on to the skin following the biopsy. Each nodule was passed twice.

The aspirates were sprayed on four slides, resulting in streaks that were fixed in alcohol. The remaining aspirate from each syringe was cleaned in a CytoLyt solution and sent for cytology.

The Bethesda system for reporting thyroid cytopathology

Implied malignancy risk and recommended clinical treatment was done according to Ali et al., 2023.[12]

SLE disease activity index (SELDAI score)

SELDAI score was classified as; No activity (SLEDAI=0), mild activity (SLEDAI= 6 to 10), high activity (SLEDAI = 11 to 19), and very high activity (SLEDAI ≥ 20).[13]

Statistical Analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS; Version 27.0. Armonk, NY: IBM Corp.). The quantitative data are presented as mean, standard deviations, and ranges when parametric, and median, interquartile range (IQR) when non-parametric. Qualitative data are reported as numbers and percentages. Chi-square test and/or Fisher exact test were used to compare groups with relation to qualitative data. The Independent t-test was employed to compare two independent groups with quantitative data and a parametric distribution, whereas the Mann-Whitney test was utilized for non-parametric data. Spearman correlation coefficients were employed to determine the relationship between two quantitative factors within the same group. A *p*-value < 0.05 was considered significant.

Results

In our study, there were 1.3% males and 98.8% females with mean age of 33.67 years. As regard clinical data, the mean systolic blood pressure (SBP) was 121.06 mmhg, diastolic blood pressure (DBP) 79.56 mmhg, and mean pulse of 77.32 bpm. By thyroid examination, 27.5% of patients had goiter and 72.5% of them had no goiter. As regard SLEDAI score, the median was 2 with a range of 0-13. The mean hemoglobin was 11.03 g/dl, TLC 6.63 k/µl, platelet count 280.8 k/µl. The CRP was 10 mg/dl, C3 130.43 mg/dl, and C4 23.3 mg/dl. (Table 1)

Table 1. Demographic and laboratory data and characteristics of the 80 studied cases.

		Total no. = 80
Age (years)	Mean ± SD	33.67 ± 10.15
	Range	18 – 57
Gender (Number and percentage)	Male	1 (1.3%)
	Female	79 (98.8%)
Systolic blood pressure (mmHg)	Mean ± SD	121.06 ± 14.64
	Range	90 – 160
Diastolic blood pressure (mmHg)	Mean ± SD	79.56 ± 9.72
	Range	60 – 100
Pulse (bPm)	Mean ± SD	77.32 ± 9.49
	Range	58 – 96

Table 1. Continued.

		Total no. = 80
Thyroid examination (Number and percentage)	No goiter	58 (72.5%)
	Goiter	22 (27.5%)
SLEDAI score	Median (IQR)	2 (0 – 5)
	Range	0 – 13
HB (g/dl)	Mean ± SD	11.03 ± 1.11
	Range	7.7 – 13.3
TLC (k/μL)	Mean ± SD	6.63 ± 1.9
	Range	3.8 – 12
Platelet (k/μL)	Mean ± SD	280.8 ± 97.82
	Range	111 – 510
CRP (mg/dl)	Median (IQR)	10(6 – 15)
	Range	1 – 45
C3 (mg/dl)	Mean ± SD	130.43 ± 31.47
	Range	76 – 199
C4 (mg/dl)	Mean ± SD	23.3 ± 9.85
	Range	6 – 56

Concerning the thyroid profile, the mean **t**hyroid-stimulating hormone (TSH) was 2.77 μIU/ml, Free T4 (FT4) 1.17 ng/dl, and FT3 2.92 pg/ml. As regard Anti thyroid peroxidase (TPO) antibodies, 24 patients (30%) were positive, and respecting thyroid hormone status, 62.5% of patients were with normal thyroid function. The thyroid US data are presented in Table 2.

Table 2. Thyroid profile and US (nodules) of the 80 studied patients.

		Total no. = 80
TSH (μIU/ml)	Median (IQR)	2.77 (1.18 – 5)
	Range	0 – 55
FT4 (ng/dl)	Mean ± SD	1.17 ± 0.33
	Range	0.48 – 2.32
FT3 (pg/ml)	Mean ± SD	2.92 ± 1.07
	Range	0.66 – 6.5
Anti TPO (IU/ml)	NEG	56 (70.0%)
	POS	24 (30.0%)
Thyroid hormones status	Normal	50 (62.5%)
	Abnormal	30 (37.5%)
Thyroid hormones status	Normal	50 (62.5%)
	Overt Hyperthyroidism	1 (1.3%)
	Overt Hypothyroidism	11 (13.8%)
	Sick euthyroid	7 (8.8%)
	Subclinical hyper	2 (2.5%)
	Subclinical hypo	9 (11.3%)
Thyroid US (Nodules)	Negative for nodules	59 (73.8%)
	Positive for nodules	21 (26.3%)
	Patients had FNAC	11 (52.4%)
	Proved malignancy by FNAC (Number and percentage)	3 (19.0%)

There was no statistically remarkable variation regarding demographic and laboratory data between the study groups. (Table 3)

There was remarkable relation of ultrasonographic changes in the form of nodular pattern between patients with normal thyroid functions and cases with abnormal thyroid functions (p< 0.007) with higher percent of thyroid nodules among patients with abnormal thyroid functions (43.3%). (Table 4).

Table 3. Comparison between patients with normal and abnormal thyroid hormone status regarding demographic and laboratory data and characteristics of the 80 studied patients.

		Thyroid hormones classification		*p*-value
		Normal No. = 50	Abnormal No. = 30	
Age (year)	Mean ± SD	33.36 ± 10.23	34.2 ± 10.17	NS•
	Range	18 – 57	18 – 53	
Gender	Male	0 (0.0%)	1 (3.3%)	NS*
	Female	50 (100.0%)	29 (96.7%)	
SBP (mmHg)	Mean ± SD	120.9 ± 14.7	121.33 ± 14.79	NS•
	Range	90 – 160	90 – 150	
DBP (mmHg)	Mean ± SD	78.9 ± 9.76	80.67 ± 9.71	NS•
	Range	60 – 100	60 – 100	
Pulse (bpm)	Mean ± SD	76.86 ± 9.48	78.1 ± 9.6	NS•
	Range	59 – 96	58 – 96	
Thyroid examination	No goiter	35 (70.0%)	23 (76.7%)	NS*
	Goiter	15 (30.0%)	7 (23.3%)	
SLEDAI	Median (IQR)	1 (0 – 4)	2 (0 – 6)	NS
	Range	0 – 13	0 – 12	
HB (g/dl)	Mean ± SD	10.97 ± 1.12	11.12 ± 1.1	NS•
	Range	7.7 – 13	8.9 – 13.3	
TLC (k/μL)	Mean ± SD	6.63 ± 1.76	6.64 ± 2.14	NS•
	Range	4 – 11	3.8 – 12	
Platelet (k/μL)	Mean ± SD	265.26 ± 90.44	306.7 ± 105.52	NS•
	Range	111 – 510	111 – 499	
CRP (mg/dl)	Median (IQR)	9(6 – 14)	11(9 – 17)	NS
	Range	2 – 45	1 – 39	
C3 (mg/dl)	Mean ± SD	129.5 ± 31.84	131.97 ± 31.33	NS•
	Range	76 – 199	83 – 187	
C4 (mg/dl)	Mean ± SD	24.58 ± 10.86	21.17 ± 7.59	NS•
	Range	6 – 56	10 – 37	

p > 0.05 is not significant (NS). *: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test.

Table 4. Comparison of anti TPO, thyroid U/S, and FNAC results between patients with normal and abnormal thyroid hormone classification.

		Thyroid hormones classification		*p*-value*
		Normal No. = 50	Abnormal No. = 30	
Anti TPO (IU/ml)	NEG	35 (70.0%)	21 (70.0%)	NS
	POS	15 (30.0%)	9 (30.0%)	
Thyroid U/S (nodules)	NEG	42 (84.0%)	17 (56.7%)	0.007
	POS	8 (16.0%)	13 (43.3%)	
FNAC	Not biopsed	45 (90.0%)	24 (80.0%)	NS
	Biopsed	5 (10.0%)	6 (20.0%)	
Proved malignancy by FNAC	Negative	49 (98.0%)	28 (93.3%)	NS
	Positive	1 (2.0%)	2 (6.7%)	

$p > 0.05$ is not significant (NS). *: Chi-square test.

Table 5 shows that there was no remarkable correlation between SLEDAI score and the other studied parameters. There was a positive relation between SLEDAI score and number of cases with TNSs and positive relation between SLEDAI score and malignancy as proved by FNAC. (Table 6)

Table 5. Correlation between SLEDAI score and the other studied parameters.

	SLEDAI	
	r	*p*-value
Age (years)	0.085	NS
SBP (mmHg)	-0.090	NS
DBP (mmHg)	-0.032	NS
Pulse (Bpm)	-0.071	NS
TSH (μIU/ml)	-0.190	NS
FT4 (ng/dl)	0.133	NS
FT3 (pg/ml)	-0.121	NS
HB (g/dl)	-0.003	NS
TLC (k/μL)	-0.024	NS
Platelets (k/μL)	-0.021	NS
CRP (mg/dl)	-0.017	NS
C3 (mg/dl)	-0.145	NS
C4 (mg/dl)	0.176	NS

Spearman correlation coefficients. $p > 0.05$ is not significant (NS).

Table 6. Relation between SLEDAI score and the other studied parameters.

		SLEDAI		≠*p*-value
		Median (IQR)	Range	
Gender	Male	0 (0-0)	0-0	NS
	Female	2 (0-5)	0-13	
Thyroid hormones classification	Normal	1 (0-4)	0-13	NS
	Abnormal	2 (0-6)	0-12	
Anti TPO (IU/ml)	NEG	2 (0-5)	0-12	NS
	POS	1 (0-5)	0-13	
Thyroid U/S (nodules)	NEG	1 (0-4)	0-13	0.041
	POS	3 (1-7)	0-10	
FNAC	Negative	2 (0-4)	0-13	NS
	Positive	5 (0-8)	0-10	
Malignant nodules by FNAC	Negative	2 (0-4)	0-13	0.006
	Positive	9 (8-10)	8-10	

p > 0.05 is not significant (NS). ≠: Mann-Whitney test.

Discussion

TNS are distinct thyroid lesions that radiologically different from the neighboring parenchyma. With the growing usage of sensitive imaging modalities, such as neck visualization, demand attention, and a significant number of TNSs arose.[14]

The current investigations documented that the malignancies prevalence in SLE differs greatly; hence a reliable and weighted analysis of the standardized incidence rate is important.[9]

Our study aimed to detect TNSs prevalence in SLE cases and the prevalence of malignant nodules by TI-RAD score and FNAC in a sample of Egyptian population. Our study revealed that the percent of TNSs among our cases with SLE was 26.3% (21 out of 80 patients). This is in line with findings of a study by *Antonelli et al., 2010,* [15] who found that the TNSs prevalence in Hispanic cases with SLE was 25%. Also Quintanilla-Flores et al., 2013,[16] reported that in SLE cases, TNSs prevalence was 27%. This wide variety of results between previous studies regarding thyroid nodule distribution in SLE patients may be due to different population and demographic data.

Patients with SLE may develop thyroid nodules due to the fact that SLE is an autoimmune condition that can lead to thyroid dysfunction, such as Hashimoto's thyroiditis. This is featured by inflammation and can promote nodule formation and some medications used to treat SLE can have thyroid-related side effects, contributing to changes in the thyroid structure and function.[16]

In our study, we found that 26.3% of the patients had nodular goiter (21 out of 80), 52.4% from them (11 out of 21) showed suspicious nodules by ultrasound and underwent FNAC, 24% of them (3 out of 11) showed malignant transformation in the form of (one papillary, one medullary and one follicular carcinoma.

In our study, the incidence of thyroid carcinoma (TC) was 3.75% (3 out of 80 patients) and 14.2% (3 out of 21 patients) in patients with thyroid nodules. This comes in agreement with several previous studies. The study by Grussendeorf et al., 2022,[14] found that TC prevalence in unselected TNS individuals was in a range of 1-5%. Also, the study by Xu et al., 2024,[18] found that TC incidence among TNSs cases was 5- 15%. However, the study by Dreyer et al., 2011,[19] failed to demonstrate a link between SLE and thyroid cancer and SLE. In addition, Kang et al., 2010,[20] found that there was no relation between SLE and thyroid cancer.

In contrast to the study by Bernatsky et al., 2013,[10] which included a large cohort study, (1848 SLE patients), noted an elevated risk for thyroid malignancy in SLE cases. Theses variation in the study findings may be attributed

to differences in study designs, regular follow up annually of patients and due to contribution of large number and multiple populations with various races and ethnicities in different countries. These are in contrast to our study which included only an Egyptian population.

Immunosuppressive therapy used in SLE like corticosteroids and other immunosuppressants in SLE management may reduce the immune system's ability to determine and eliminate malignant cells, potentially elevating cancer risk.[10]

In our study, we found higher substantial number of TNSs cases among the group with abnormal thyroid functions; 13 patients (43.3%) versus the group with normal thyroid functions 8 patients (16%). Moreover, in the study by, Li et al., 2023,[21] included 2460 subjects found that abnormal TSH values were related with elevated TNS risk.

In contrast to our study, Gharib et al., 2008,[2] concluded that thyroid nodule had no relationship with thyroid function tests. Such variation between study findings may be attributed to differences in study designs, participants' criteria and race or ethnicity.

Thyroid nodules are more prevalent in patients with abnormal thyroid function due to several factors like underlying diseases which are conditions like Hashimoto's thyroiditis or Graves' disease which often cause abnormal thyroid function and can lead to structural changes in the thyroid causing increased nodule formation [22]

Also, hormonal influence which results in abnormal thyroid hormone levels can stimulate the growth of thyroid cells, potentially leading to the development of nodules. Moreover, thyroid dysfunction may create a metabolic environment that fosters nodule growth, particularly in the presence of inflammation or autoimmune responses.[22]

In our study, the results did not reveal any significant correlation between SLE disease activity in terms of SLEDAI score and thyroid hormone status, autoimmunity (Anti TPO). These findings are consistent with those of Mader et al., 2007,[23] who failed to determine relationship between anti-thyroid antibodies (ATA) positivity and SLEDAI score.

In contrast, a study included 167 individuals with SLE found that cases with hypothyroidism and SLE had a substantially greater SLEDAI score than those with subclinical hyperthyroidism and euthyroid.[24] Moreover, another study included 63 cases with SLE patients showed that Hashimoto's thyroiditis is correlated with disease activity.[25]

In our study we found a positive relation between SELDAI score and thyroid nodules, and positive relation between SELDAI score and the prevalence of malignancy.

Our population showed that 11 patients (13.8%) with overt hypothyroidism, 9 patients (11.3%) with subclinical hypothyroidism and 1 patient (1.3%) with overt hyperthyroidism. Our findings are in line with those of Kumar et al., 2012,[26] Liu et al., 2018,[24] in which in SLE cases, the rates of hypothyroidism ranged 3.9-17.4%, and hyperthyroidism was 0.5-8%. The substantial variation between these researches is most likely owing to changes in sample size, study methodology, and ethnic groups.

In the current study, the most prevalent thyroid condition was overt hypothyroidism with 13.8%; this agreed with findings of other studies, that determined overt hypothyroidism as a common thyroid disorder in lupus cases (15–19%).[27, 28] In contrast to our study findings, Luo et al., 2018,[29] meta-analysis study of 44,170 controls and 10,500 cases with SLE found that subclinical hypothyroidism was more prevalent in SLE cases than in controls. This discrepancy could be due to variations in the study population and design.

Regarding anti-thyroid antibodies (Anti TPO), in our cases, the percent of patients with positive levels were 30% (24 out of 80). Also, Pan et al, 2015,[30] in their meta-analysis study, included 1076 SLE patients showed that the percentage of positive Anti TPO level was (20.4%). Moreover, Miller et al., 1987,[31] showed that 18% of their cases had high anti TPO antibody titers. And, Pyne et al., 2002,[32] also reported that the incidence of thyroid antibodies was 14% which were anti TG and anti TPO antibodies. In Egypt, El-Sharif et al., 2004,[33] in their case control study, included 132 SLE patients; found that the percent of patients with SLE and positive Anti TPO was 15%. This

difference with our study findings in an Egyptian population may be related to patients' number, sensitivity of the assay and age of patients.

In conclusion, our study revealed that the percent of thyroid malignancy among SLE cases was the same as in the general population, so that SLE itself did not increase the risk of thyroid malignancy. Also, the percent of TNSs among cases with SLE was the same as in the general population. Activity of SLE in terms of SLEDAI score has relation with TNSs and malignancy. Cases with SLE and TNSs are more susceptible to thyroid dysfunctions.

Author Contributions

Experimental design: HMA and RSA. Data interpretation: INA, MRM, and RSA. Statistical analysis: HMA and INA. Clinical examination: INA and MRM. Laboratory tests: INA. Writing and revision: All authors. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Ethical approval

The protocol of the study was reviewed and accepted by the Research Ethics Committee of the Faculty of Medicine, Ain shams University (approval: FMASU MD 244/2022).

Informed consent

A signed consent form was obtained from each study participant.

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