Survey of Pap Smear in Women with Systemic Lupus Erythematosus

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ABSTRACT:

BACKGROUND:

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder affecting mainly young women during childbearing years.

OBJECTIVE:

To assess the prevalence of cervical dysplasia in a group of Iraqi women with SLE and study the relationship between results of Pap smear and HPV DNA test with disease activity, disease duration and use of immunosuppressant drugs.

PATIENTS AND METHODS:

A case controlled study was conducted on 55 women with SLE and 55 healthy controls. Full history was taken and complete physical examination including extensive gynecological evaluation was done for both groups. High vaginal swab and culture, Pap smears and HPV PCR test were done to them.

RESULTS:

Patients with SLE were more likely to have cervical dysplasia than control (P=0.022) with 2.1 folds increased risk. HPV infection was found to have no statistically significant difference between both studied groups (P>0.15). The C1N1 changes were significantly associated with high SLEDAI scores (P=0.030) and longer disease duration (P= 0.027). There was no significant correlation neither with the dose nor with the duration of use of immunosuppressant medications and Pap smear findings (P> 0.05).

CONCLUSION:

The prevalence of cervical dysplasia was higher in SLE patients than controls. Patients with SLE were more likely to have abnormal Pap smear findings which significantly and directly associated with disease duration and disease activity than controls.

KEYWORDS: Pap smear, cervical dysplasia, systemic lupus erythematosus

INTRODUCTION:

Systemic lupus erythematosus (SLE) is an autoimmune connective Tissue disease with a broad spectrum of clinical presentations with predilection to involve women of childbearing age. SLE has variable clinical features ranging from benign skin & joint involvement to organ & life threatening kidney and CNS disease. (2)

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In Iraq, the prevalence of SLE was estimated to be one patient per 1867 of population, one per 1127 of the total female population and for women aged between 10 and 49 years it was one per 616. [3].

Lupus patients with chronic HPV infection have an increased risk of cervical intra epithelial neoplasia [4]. SLE patients have an increased risk of malignancies compared with controls specially lymphoma, lung, hepatobiliary, and vulvovaginal malignancies. There is also very good evidence that cervical dysplasia is increased in women with SLE. [5]

Cervical cancer ranks as the 3rd most common cancer among women and it ascends one step

to be the 2nd most common cancer when the age is limited between 15 to 44 years. According to the latest Iraqi Cancer Registry records (2008), cervical cancer ranks the 8th among the most common female cancers in Iraq accounting for 0.8% of total female malignancies [6].

Most cervical cancers begin with pre-cancerous changes like cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), and cervical dysplasia. [7] CIN is an easily curable when detected early and may be self limiting. However, a small percentage of cases may progress to become cancerous usually cervical squamous cell carcinoma (SCC), if left untreated [8].

Histologic grading of CIN is based on the percentage of the epithelium occupied by abnormal cells. The epithelium is divided into thirds [9]

1. CIN : low grade lesion. There is atypical cellular changes in the lower third of the epithelium. HPV effects often detectable.
2. CIN 2: a high grade lesion. There is moderately atypical cellular changes confined to the basal two-thirds of the epithelium with normal epithelial maturation.
3. CIN 3 is also considered a high grade lesion. It refers to severely atypical cellular changes occupying more than two-thirds of the epithelial thickness, and includes full-thickness lesions (severe dysplasia or carcinoma in situ).

Human papilloma virus infections (HPVs) are the most important risk factor for cervical cancer [10,11]. There is an increased prevalence of high-risk HPV (HR-HPV) and multiple HPV infections in SLE patients, especially, HPV-16. those patients with SLE and high HPV-16 viral load had more SIL than those with a low HPV-16 viral load. [12] At least 15 HPV types are associated with malignancy [11]. The types 16 and 18 are the most common types found in cervical squamous cell carcinoma, accounting for more than 70% of cases [13].

Direct detection of HPV DNA can be done histologically by either by Nucleic acid amplification by polymerase chain reaction (PCR). Or Hybrid capture (HC) system, which screens five low-risk HPV types and 13 high-risk HPV.[14] Current screening strategies are used to identify pre cancerous disease, using pap smears, detection of oncogenic HPV genotypes, or even direct visual inspection using acetic acid. [15] The Pap smear test proved of extreme importance in the early detection, and in the prognosis of cervical cancer [16] in the United States which helped reduce Mortality rates in the past decade.

The most widely used system for describing Pap test results is the Bethesda System (TBS) [17]. There are 3 main categories, some of which have sub-categories:

- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality
- Other malignant neoplasms

since there is a good evidence that cervical dysplasia is increased in women with SLE, The American College of Obstetricians and Gynecologists (ACOG) recommends yearly cervical cancer screening in immunocompromised women, regardless of age, and they would advise yearly pap testing in all women exposed to immunosuppressive therapies (particularly cyclophosphamide). [5]

AIM OF STUDY:

To assess the prevalence of cervical dysplasia in adult of Iraqi women with systemic lupus erythematosus. And to study the relationship between result of Pap smear and HPV DNA test and clinical parameter such as disease activity, disease duration and use of immunosuppressant drugs.

PATIENTS AND METHODS:

A case-control study was conducted at the Rheumatology unit, Department of Medicine at Baghdad Teaching Hospital from September 2014 to May 2015. Fifty five lupus patients and 55 healthy controls were evaluated. All women had a gynecologist examining them and high vaginal swab and culture were done and these were sent to central public health lab For Pap smear and HPV DNA test (PCR). Pap smears were evaluated and assessed using the Bethesda System (TBS) 2001. Blood sample was obtained

for measurement of complete blood counts, antinuclear antibodies (ANA), anti-double stranded DNA antibodies , complements components, antiphospholipid antibodies, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus antibody (anti HCV antibody), human immunodeficiency virus (HIV) and venereal disease research laboratory(VDRAL) test. Urine examination was done for measurement of protein, white blood cells (WBC), red blood cells (RBC) and cellular casts. SLE disease activity was measured using systemic lupus erythematosus disease activity index (SLEDAI).

A signed consent was taken from the individuals in both groups for admission in the study. Patients who had overlapping features of other connective tissue diseases, pregnant women, women with total hysterectomy and virgins were excluded from the study.

Statistical analysis:

Data were entered and analyzed using the Chi square and Fishers exact test. Student's t test was used to compare means. Spearman's rho correlation test was used to assess the correlation of the Pap smear findings with the dose and duration of treatment used.

RESULTS:

Table 1: Distribution Human papilloma virus and Pap smear findings

Variable		Group				P
		Cases (n=55)		Controls (n=55)		
		No.	%	No.	%	
HPV	Positive	2	3.6	0	0.0	0.15
	Negative	53	96.4	55	100.0	
Pap Smear	CIN 1, Dysplastic changes	5	9.1	0	0.0	**0.022***
	Squamous metaplasia	9	16.4	4	7.3	0.15
	Chronic non-specific cervicitis	31	56.4	23	41.8	0.13
	Normal	10	18.2	28	50.9	**< 0.001**

Table 2: Comparison between positive Pap smear findings and negative for intraepithelial neoplasia for both studied groups.

Pap smear Finding	Group				***Risk ratio (95% CI)***	***P***
	Cases (n= 55)		Controls (n= 55)			
	No.	%	**No.**	%		
Positive finding	5	9.1	0	0	2.10 (1.72 – 2.57)	**0.022**
Negative for intraepithelial neoplasia	50	90.9	55	100		
Total	55	100.0	55	100.0		

Table 3. Relationship between Pap smear findings and HPV infection

Pap smear finding	HPV Positive		HPV Negative	
	No.	%	No.	%
CIN 1, Dysplastic changes	2	40.0	3	60.0
Squamous metaplasia	0	0.0	9	100.0
Chronic non-specific cervicitis	0	0.0	31	100.0
Normal	0	0.0	10	100.0

P. value = 0.001

Table 4: Comparison of mean disease activity among SLE patients with different Pap smears findings

Pap smear finding	No. of patients	Mean SLEDAI ± SD
CIN 1, Dysplastic changes	5	17.0 ± 7.0
Chronic non-specific cervicitis	31	11.9 ± 6.2
Squamous metaplasia	9	9.4 ± 5.7
Normal	10	7.9 ± 2.7
ANOVA, P. value = 0.030 (between groups), and 0.040 (within groups)		

Table 5: Comparison of mean disease duration among SLE patients with different Pap smears findings.

Pap smear finding	No. of patients	Mean disease duration ± SD (year)
CIN 1, Dysplastic changes	5	10.2 ± 4.8
Chronic non-specific cervicitis	31	3.6 ± 2.2
Squamous metaplasia	9	6.2 ± 0.6
Normal	10 ± 1.4	5.2 ± 1.4
ANOVA, P. value = 0.022 (between groups), and 0.027(within groups)		

Table 6: Results of logistic regression analysis for adjustment of possible confounding effect

Variable	*B*	S.E.	df	Exp (B) Odds ratio [95%CI]	Sig.
SLE	1.2	0.63	1	**3.35** [1.28 – 6.38]	**0.013**
Age at marriage	0.21	0.08	1	1.23 [0.87 – 4.62]	0.062
Gravidity	0.32	0.18	1	**1.37** [1.02 – 2.89]	**0.048**
Parities	0.27	0.12	1	1.30 [0.91 – 4.23]	0.051
Abortion	0.42	0.21	1	**1.42** [1.10 – 5.28]	**0.022**
HPV	0.10	1.10	1	1.09 [0.65 – 4.29]	0.081
Constant	3.9	0.74	1	-	**0.000**
Dependent variable : CIN 1 Dysplastic changes (positive pap smear finding) Adjustment for Variable(s) entered on step 1: SLE, Age at marriage, Gravidity, Parities, Abortion, HPV Test.					

DISCUSSION:

To the best of our knowledge, this was the first study in Iraq, assessing the prevalence of cervical dysplasia in Iraqi women with SLE, studying the relationship between result of Pap smear and HPV DNA test and the clinical parameter of those patients.

In this study, ANA test was positive in vast majority (94.55%), which agrees with previous estimates of ANA negative SLE of 5 – 8.9%.

The current study found a positive HPV infection (high risk HPV, 16, 18), in only 2 SLE patients (3.6%), and none of the controls. Despite being statistically insignificant, this difference is still of a clinical importance. SLE patients had higher risk of cervical dysplasia or cancer in the presence of HPV because of their additive risk defects in innate immunity, and the use of immunosuppressive drugs [18]. The findings of the current study was lower than that reported in a previous Mexican study in which HPV positivity was found in 14.7% of SLE patients, and 30.8% of controls [19]. Other studies found that 54% and 37.5% of SLE patients had cervical HPV infections [20-22]. The reason for these differences might be attributable to the high risk sexual behavior in other countries. SLE patients were more likely to have CIN1, epithelial dysplasia (5 patients (9.1%)) than controls, (P=0.022). In a previous study CIN1 was found in 5.8% of SLE patients [23]. The Risk of abnormal Pap smear is 2.1 the increased risk is consistent with that reported in previous studies; [17,21, 24, and 25]. The risks, however, were different due to different in sample size, ethnicity and more prevalent with HPV infection.

The current study found a positive significant association between the disease duration and the abnormal Pap smear findings, patients with dysplastic changes had the longer disease duration and higher mean SLEDAI of 17 ± 7, compared to 7.9 ± 2.7 in those with normal Pap smears. These findings are consistent with other published studies [26, 27].

None of the medications showed significant correlation with the findings of pap smears, which is against what had been reported in some studies [28,29] which might attributed to the fact that all the patients in our study were on one or more of these medications, not to mention the small sized samples. Still, other studies reported no significant association between use of immunosuppressive medication and Pap smear findings [21, 25, 30].

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CONCLUSION:

Patients with SLE were found to have higher Risks for cervical dysplasia, abnormal pap smears and HPV infections than matched controls, And the Immunosuppressive drugs; steroids and HCQ, were obviously-yet, not statistically- associated with higher proportion of CIN1 (dysplastic changes) in patients with SLE.

Author contributions

All authors made substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors give final approval of the version to be submitted and any revised version.

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