ORIGINAL ARTICLE

Prevalence of *Chlamydia trachomatis* endocervical infection in systemic lupus erythematosus patients and evaluation of the risk for HPV-induced lesions

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Abstract *Chlamydia trachomatis* (CT) is the most common bacterial cause of sexually transmitted disease. It has been associated with arthritis and it is a risk factor for human papillomavirus (HPV)-induced lesions. There are few studies on the frequency of CT infection among systemic lupus erythematosus (SLE) patients. The aim of this study was to determine the prevalence of endocervical CT infection among SLE patients and evaluate whether or not CT infection is a risk factor for HPV-induced lesions. A cross-sectional study included a group of patients who fulfilled the American College Rheumatology criteria for a definite diagnosis of SLE and a control group of non-SLE female individuals from Bahia, Brazil. Polymerase chain reaction was used on endocervical swab specimens to test for CT; a gynecological examination including a cervical cytology and biopsy was done for the identification of HPV lesions. A total of 105 SLE patients were studied, and the control group was composed of 104 age-matched apparently normal women. The prevalence of CT endocervical infection was 3.0 % [confidence interval (CI) 95 % = 0.6–8.0 %] in the SLE group and 5.0 % (95 % CI = 2.0–11.0 %) in the control group; the prevalence ratio was 0.60 (95 % CI = 0.1–2.5). The prevalence of vulvar condyloma was higher among SLE patients (11.0 vs. 1.0 %, $p < 0.001$), as were the prevalences of low-grade lesion (12.0 vs. 1.0 %, $p < 0.001$) and cervical intraepithelial neoplasia 1 (9.0 vs. 1.0 %, $p = 0.02$). There was no association between the presence of HPV lesions and CT infections. However, the small number of patients with CT prevents a definite conclusion from being drawn. The prevalence of endocervical CT infection in women with SLE is low and similar to that of the normal population. This suggests that this infection has no role in the pathogenesis of SLE or the development of HPV-induced lesions.

Keywords *Chlamydia trachomatis* · Systemic lupus erythematosus · Human papillomavirus · Polymerase chain reaction

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Introduction

The prevalence of *Chlamydia trachomatis* (CT) infection varies between 5.0 and 21.0 % in the USA [1] and 3.0–10.0 % in Europe [2–4]. In Brazil, it ranges between 3.0 and 21.0 % [5–8]. These percentages vary based on the socioeconomic status and/or genetic background of the studied population, the age of the patients, from where the specimen was collected [urethra, vagina, cervix, urine, blood [9]] and the diagnostic method utilized. CT causes a variety of urogenital and extra-genital diseases such as pelvic inflammatory disease (PID) and blindness. It has also been associated with rheumatic disorders, particularly

spondyloarthritis [10–15]. In addition, CT can facilitate the transmission of HIV (it increases the risk of HIV infection by 2–4 times) [14] and it is a possible cofactor for the progression of HPV-induced lesions and cervical cancer [16–18].

It is well known that patients with systemic lupus erythematosus (SLE) have a higher prevalence of certain infections [19–22] including HPV [23, 24], either by the disease itself or by the use of immunosuppressive drugs, but there has been no study on the prevalence of endocervical CT infection in relation to this condition.

The aim of this study was to investigate the prevalence of endocervical CT infection among SLE patients to and assess whether or not CT infection is a risk factor for HPV-induced lesions.

Materials and methods

This is a descriptive, cross-sectional study. A group of SLE female patients and an age-matched control group of healthy women followed at the outpatient clinics of the Escola Bahiana de Medicina e Saúde Pública in Salvador, Brazil, were included in this study. All SLE patients fulfilled the criteria for a definite diagnosis of SLE based on the guidelines from the American College of Rheumatology [25]. They were recruited between 2009 and 2010.

The age of the studied population ranged from 18 to 65 years; all patients had had sexual experience. Exclusion criteria were psychiatric disorders, pregnancy, early postpartum period, hysterectomy, or the use of any antibiotic in the 30 days prior to the examination. In the control group, individuals with any articular symptoms were excluded.

The study was approved by our institution's Ethics Committee. All patients signed an informed consent form prior to entry in the study. Each patient gave information about their medical history, household income and use of immunosuppressive drugs; each patient also underwent a physical examination and a gynecological evaluation which included colposcopic and cytology exams. A cervical biopsy was performed out in cases with an abnormal colposcopy. Colposcopic results were classified according to the International Federation for Cervical Pathology and Cytology [26]; for statistical analysis purpose, results were categorized into groups of inflammation, low-grade lesion [this group includes irregularities such as HPV and cervical intraepithelial neoplasia, (CIN) 1], high-grade lesion (CIN 2, CIN 3) and invasive cancer [27]. The biopsy results were analyzed in the following categories: cervical intraepithelial CIN 1, CIN 2 and CIN 3, cancer, invasive cervical cancer [28] and vulvar intraepithelial neoplasia (VIN 1, VIN 2 and VIN 3) [29].

Endocervical smears were collected using a sterile swab (J. Prolab® and CRAL®). Polymerase chain reaction (PCR) testing was used to test for CT at the Advanced Laboratory of Public Health of the Oswald Cruz Foundation. The endocervical smears were collected in 400 μl of TE [10 mM Tris–HCl pH 8.0 and 1 mM ethylenediamine tetra-acetic acid (EDTA)] [30]. DNA extraction was made by Qiagen kit (Qiamp DNA Mini Kit®). The samples were maintained at −20 °C until used. The primers KL1—5 TCCGGAGCGAGTTACGAAGA 3′ and KL2—5′AAT CAATGCCCGGGATTGGT 3′ were used to amplify a 241 bp fragment of chlamydial plasmid (KL1 and KL2) [31]. Standard reaction conditions were used to amplify each reaction for a final volume of 25 μl. The reaction was composed of 13 μl Top Taq Master Mix (Qiagen®) (2×), 1 μl of KL1 and KL2 primers (10 pmol/μl), 2.5 μl of CoralLoad Concentrate (10×), 2.5 μl of RNAase-free water and 5 μl of DNA samples template (average 50 ng/ μl). The amplification was done in an Applied Biosystems Veriti™ Thermal Cycler with the following cycling temperatures: initial heating at 94 °C for 5 min, 35 cycles of denaturation at 94 °C for 20 s, annealing at 57 °C for 20 s and extension at 72 °C for 1 min. In order to visualize the PCR product, a 2 % agarose gel electrophoresis was applied and then stained with ethidium bromide.

The prevalence and prevalence ratios (Mantel–Haenszel) were presented in 95 % confidence intervals (CI). Quantitative variables were presented as mean ± SD or median and interquartile range, and qualitative variables were expressed as percentages. Statistical tests were chosen after normality tests. Means were compared with the Student's t-test or Mann–Whitney test, depending on the normality of the variable. Relationships between qualitative variables were studied using chi-square or Fisher's exact tests. Logistic regression was used to estimate the association between the CT test and each possible risk factor. It was estimated that 87 women with SLE were needed to calculate the prevalence of CT endocervical infection with a 95 % CI (alpha of 0.05), considering an estimated prevalence of 6.0 %. Statistical analysis was performed with SPSS for Windows, version 17.0 (SPSS, Chicago, IL).

Results

Socio demographic and behavioral characteristics of the studied population

There were 105 women in the SLE group and 104 in the control group. The mean age was 38 ± 11 in SLE group and 36 ± 11 in the control group, $p = 0.08$. There was a statistically significant difference between the household income of the two groups (44.0 vs. 62.0 %, $p = 0.01$), number of current smokers (4.0 vs. 11.0 %, $p = 0.04$) (Table 1) and age at first sexual intercourse (20 ± 4 vs.

Table 1 Socio-demographic and behavioral characteristics of the patients in the two study groups: systemic lupus erythematosus (SLE) and control

SD standard deviation, [†] t-test; * chi-square test; [a] Brazilian minimum wage: US $285 per month; ** Fisher's exact test; $p < 0.05$ = statistically significant

Variables	SLE group (N = 105)		Control group (N = 104)		p value
	N		N		
Age (mean ± SD)	105	38 ± 11	104	36 ± 11	0.08[†]
Education ≤ 8 years (%)	40	38	33	32	0.33*
Education > 8 years (%)	64	62	70	68	0.33*
Income = 1 minimum wage[a] (%)	59	56	39	37	0.01*
Income > 1 minimum wage[a] (%)	46	44	65	62	0.01*
Current smokers (%)	4	4	12	11	0.04**

18 ± 4, $p = 0.01$) (Table 2). The mean duration of SLE was 9 ± 6 years. The SLE patients were using the following drugs: 59 % prednisone, 24 % azathioprine, 9 % mycophenolate mofetil, 2 % tacrolimus, 2 % leflunomide and 1 % cyclosporine.

Prevalence of *Chlamydia trachomatis* infection (PCR)

The prevalence of CT endocervical infection was 3.0 % (95 % CI = 0.6–8.0 %) in the SLE group and 5.0 % (95 % CI = 2.0 %–11.0 %) in the control group, $p = 0.49$ (Table 2); the prevalence ratio was 0.60 (95 % CI = 0.1–2.5), $p = 0.47$.

In the control group, the following variables were analyzed using univariate analysis and found not to have statistical significance to CT infection: age at first sexual intercourse, number of partners, condom use and history of sexually transmitted diseases (STD) and cervical ectopy.

Prevalence of HPV-induced lesions

The prevalence of vulvar wart (condyloma) was higher among SLE patients than the control group (11.0 vs. 1.0 %, $p < 0.001$), as was the prevalence of low-grade intraepithelial lesion (12.0 vs. 1.0 %, $p < 0.001$) and CIN 1 (9.0 vs. 1.0 %, $p = 0.02$) (Table 3). Curiously, all SLE patients with HPV-induced lesions tested negative for CT infection.

Discussion

This study demonstrates for the first time the prevalence of endocervical CT infection among SLE patients. Based on the higher prevalence of infections observed in SLE patients secondary to the disease itself and/or the use of immunosuppressive drugs as well as on the described association of CT infection and the development of rheumatic diseases, a greater prevalence of uterine endocervical CT infection was expected in those patients. However, this study found the prevalence of CT endocervical infection to be similar in the SLE and control groups. Previous studies on women without SLE show similar findings [1, 2, 4, 6]. Aside from the age at first sexual activity (which was higher among SLE patients), other risk factors (current condom use, hormonal contraceptive use, number of partners and history of STD) for CT infection were similar between the two groups. Perhaps the higher concentrations of gamma interferon in frequently observed in SLE plasma [32, 33] are able to hold off the CT infection [34–37].

The hypothesis of molecular mimicry between microbial antigens and self-antigens has been described in several auto-immune conditions such as reactive arthritis, rheumatic fever and primary biliary cirrhosis (PBC). The present study, which finds the prevalence of CT infection to be similar between women with SLE and the normal population, suggests that this infectious agent has no role in

Table 2 Gynecological and obstetric features and prevalence of *Chlamydia trachomatis* (CT) endocervical infection in the two study groups: systemic lupus erythematosus (SLE) and control

SD standard deviation, STD sexually transmitted disease, IQ interquartile range, [†] t-test, [††] Mann–Whitney test, * chi-square test, ** Fisher's exact test, $p < 0.05$ = statistically significant

Variables	SLE group (N = 105)		Control group (N = 104)		p value
	N		N		
Age at first sexual intercourse (mean ± SD)	105	20 ± 4	104	18 ± 4	0.01[†]
Number of sexual partners (median, IQ)	105	2 (1–4)	104	3 (2–4)	0.11[††]
Current condom use (%)	14	13	15	14	0.82*
Hormonal contraceptive (%)	7	7	5	5	0.56*
Previous STD (%)	23	22	13	12	0.07*
Parity (median, IQ)	104	1 (0–2)	104	2 (1–2)	0.25[††]
Number of abortions (median, IQ)	104	0 (0–1)	104	0 (0–1)	0.32[††]
Genital CT infection (%)	105	3	104	5	0.49**

Table 3 Cytologic and histologic findings in the two study groups: systemic lupus erythematosus (SLE) and control

Variables	SLE group (N = 105)		Control group (N = 104)		p value
	N	%	N	%	
Cytology (Pap smear)					
Inflammation	55	52	49	47	0.45*
ASCUS	1	1	0	0	1.00**
LGSIL	13	12	1	1	<0.001**
HGSIL	4	4	0	0	0.12**
Histology					
Cervical wart	3	3	0	0	0.25**
Vaginal wart	7	7	0	0	0.01**
Vulvar wart	12	11	1	1	<0.001**
CIN 1	9	9	1	1	0.02**
CIN 2	1	1	0	0	1.00**
CIN 3	1	1	0	0	1.00**
VIN 2	1	1	0	0	1.00**
VIN 3	1	1	0	0	1.00**
Vulvar invasive squamous carcinoma	1	1	0	0	1.00**

* Chi-square test, ** Fisher's exact test, *ASCUS* atypical squamous cells of undetermined significance, *LGSIL* low-grade intraepithelial squamous lesion, *HGSIL* high-grade intraepithelial squamous lesion, *CIN* cervical intraepithelial neoplasia, *VIN* vulvar intraepithelial neoplasia, $p < 0.05$ = statistically significant

the pathogenesis of SLE. Leung et al. [38] researched the relationship between Chlamydia infection and PBC through serological tests (immunoblotting) and failed to demonstrate any association. Moreover, 20 SLE serum samples were included in that study and none had reactivity to CT. Similarly, Keat et al. [12] while studying the evidence of CT infection in sexually acquired reactive arthritis (SARA) used SLE, rheumatoid arthritis, ankylosing spondylitis and healthy male sera as controls. The serologic IgG antibody titers to CT in these control groups were essentially similar but they differed markedly from that in the SARA group. In another study, Kitumnuaypong et al. [9] performed a PCR analysis for CT 16srRNA and major outer membrane protein (MOMP) on DNA extracted from peripheral blood mononuclear cells in 28 SLE patients. None were positive for CT.

The higher prevalence of HPV-induced lesions among the SLE group was in agreement with the findings of other studies [23, 24, 39, 40]. Although an association has been described between HPV-induced lesions and CT infection in patients without SLE, this study found no such association. It has been speculated that CT promotes HPV persistence, leading to the development of HPV-induced lesions and even cervical cancer [14, 17, 18, 41–43]. However, this subject is a matter of controversy in the literature [44–48].

An unexpected finding of this study was the absence of association between HPV lesions and CT infection. However, it should not be interpreted as if CT confers protection against HPV infection since in previous studies from our institution which included the same population of

patients we demonstrated a prevalence of HPV infection by PCR of 80 % and some of the patients infected by CT also had HPV in endocervical smear [49]. Moreover, evidence about the role of CT infection on the predisposition for HPV infection working as a cofactor is subject of criticism as the odds ratio for such association in several studies are around 2 with CI very close to 1, not excluding the possibility that the association of endocervical CT and HPV infection is a simple coincidence in people sharing the same epidemiologic profile.

In conclusion, the rate of endocervical CT infection among patients with SLE is low and similar to that of non-SLE individuals, which suggests that this type of infection has no role in the pathogenesis of the SLE.

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