Factors associated with abnormal Pap results in systemic lupus erythematosus


Objective. Previous studies have suggested that women with systemic lupus erythematosus (SLE) are at greater risk for cervical dysplasia than are women in the general population. However, the factors associated with abnormal Pap test results in SLE have not been well studied. We therefore aimed to determine the factors associated with lifetime occurrence of an abnormal Pap test in women with SLE, and the influence of immunosuppressive exposure on the odds of abnormal Pap test results occurring after diagnosis of SLE.

Methods. Data were pooled from SLE cohorts from three centres. Self-report data were available on smoking, reproductive history, use of oral contraceptives (OC), history of sexually transmitted diseases (STDs) and whether the subjects had had cervical dysplasia on Pap testing. Logistic regression was used to examine the effect of these variables on the lifetime odds of cervical dysplasia. We then generated the adjusted odds ratio (OR) for the effect of immunosuppressive exposure on cervical dysplasia occurring after diagnosis of SLE.

Results. History of STDs and use of OCs were positively associated with reports of cervical dysplasia in adjusted analyses. The ORs for the effect of immunosuppressives on abnormal Pap test occurrence (adjusted for race, age, smoking, nulliparity, OC use and history of STDs) after diagnosis of SLE was 1.6 (95% CI 1.0, 2.7).

Conclusions. A history of STDs and use of OCs were associated with abnormal Pap reports in this SLE sample. Immunosuppressive exposure may confer further risk to women with SLE.

Key words: Systemic lupus erythematosus, Cervical dysplasia, Pap test.

Recent work has suggested that women with systemic lupus erythematosus (SLE) have an increased prevalence of cervical dysplasia and atypia on Pap testing compared with the general female population [1–4] but the determinants of this association are not clear. We recently estimated the prevalence (in an SLE sample) of several factors which are associated, in the general population, with risk of cervical dysplasia and neoplasia [5]. However, we did not examine whether these factors, in women with SLE, influence cervical dysplasia as they do in the general population. As well as knowing whether (and to what extent) these traditional factors do play a role in cervical dysplasia in SLE, it is also important to know whether additional factors, such as exposure to immunosuppressive medication [3], might further influence the risk. Previous studies that have examined exposure to immunosuppressive medication as a putative causative factor for cervical dysplasia in SLE [1–4] were limited because of small numbers of patients and an inability to control for the risk factors traditionally associated with cervical cancer in the general population.

Our objectives were, therefore, to determine the factors associated with lifetime occurrence of an abnormal Pap test in women with SLE, and to determine the influence of immunosuppressive exposure on the odds of abnormal Pap test results occurring after diagnosis of SLE.

Patients and methods

The study sample consisted of patients from the SLE clinic cohorts at three centres, the Montreal General Hospital, Canada, the Feinberg School of Medicine at Northwestern University, Chicago, USA and the University of Birmingham Medical School, UK. Consecutive patients with American College of Rheumatology criteria for SLE [6, 7] were enrolled in these clinic cohorts at the time when they presented for their first clinic visit. The total number of female subjects in the combined cohort was 1015. Ethical review board approval was obtained at the respective sites, with patient consent according to the review board specifications.

Information on self-reported abnormal Pap tests, and on factors traditionally associated with cervical dysplasia [smoking, reproductive history, use of oral contraceptives (OC)] were obtained. Human papilloma virus (HPV) is an infectious agent sexually transmitted to the endocervix and is an important factor in cervical dysplasia and neoplasia in women [8]. As a surrogate for the presence of HPV (and because other sexually transmitted diseases (STDs) are possibly associated with cervical dysplasia [9, 10]) we also collected information on past history of STDs.

Data on all of these factors were obtained from a patient self-report survey. For patients who had died or been lost to
follow-up, data were obtained from information in the clinical database or medical records. This was also done for 23 living Montreal patients who consented to participate but who did not wish to complete a survey.

Information about demographics (age, race) and exposure to immunosuppressive agents was collected from clinic-based records. For our analyses, we considered exposure to immunosuppressive agents as a dichotomous variable reflecting ever exposure to the agents most commonly used in SLE [11–13] during this time period (cyclophosphamide, azathioprine and methotrexate).

Descriptive statistics were calculated for the subjects. We developed logistic regression models examining the importance of our covariates (age, race, smoking, nulliparity, OC use, history of STDs) with respect to the lifetime occurrence of an abnormal Pap test in our sample. We then generated the odds ratio (OR) for the effect of exposure to immunosuppressives on abnormal Pap test results occurring after diagnosis of SLE, adjusting for the demographic factors and the other covariates shown to be important in the first set of analyses.

Results

The median age of the subjects at time of diagnosis of SLE was 32.0 yrs. At the time of this study, the median age of the subjects was 42.0 yrs, and the median duration of SLE was 9.0 yrs. In terms of race, 73.4% of the subjects were white, 17.3% were black, and the remainder were of other ethnic origin.

The number of subjects with an abnormal Pap report was 134 (13.3%). Over half of these (74) had occurred after date of diagnosis of SLE. For the 74 subjects who reported an abnormal Pap test after the diagnosis of SLE, the mean duration of SLE diagnosis of SLE. For the 74 subjects who reported an abnormal Pap test after the diagnosis of SLE, the mean duration of SLE at the time of the abnormal test was 12.1 yr (s.d. 7.9 yr). The mean age of the subjects at the time of the abnormal Pap test was 40.4 yr (s.d. 13.0 yr).

Table 1 presents the distribution of risk factors in the sample. Table 2 presents the unadjusted and adjusted ORs and 95% confidence intervals (CI) for the exposures of interest. History of STDs and use of OCs were associated with lifetime odds of abnormal Pap reports in the univariate analyses. The adjusted analyses (which took into account concomitantly the effects of smoking, nulliparity, OC use, STD history and also age, race and centre) produced similar estimates. These analyses did not include exposure to immunosuppressives as the outcome represented lifetime history of abnormal Pap reports, including the time before a patient developed SLE.

The percentage of the cohort that had been exposed to immunosuppressives at any time since their SLE diagnosis was 41.3%. The unadjusted OR for the effect of immunosuppressive exposure on abnormal Pap test results occurring after diagnosis of SLE was 1.2 (95% CI 0.7, 1.9). The OR for the effect of immunosuppressive exposure on abnormal Pap test results occurring after diagnosis of SLE, when adjusted for smoking, nulliparity, OC use, STD history, age, race and centre, was 1.6 (95% CI 1.0, 2.7). For specific immunosuppressives (cyclophosphamide, azathioprine and methotrexate), the adjusted odds ratios appeared similar in terms of direction and magnitude of effect; however, because of the lower number of individuals exposed to specific agents, the confidence intervals were less precise than when immunosuppressives were included as one variable in the model. The adjusted ORs for each specific immunosuppressive were as follows: cyclophosphamide OR 1.3 (95% CI 0.8, 2.1), azathioprine OR 1.2 (95% CI 0.8, 2.0) and methotrexate OR 1.1 (95% CI 0.5, 2.2).

Table 1. Covariate data for subjects in the combined lupus cohort (n = 1015)

<table>
<thead>
<tr>
<th>Factor</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco use (ever smoked)</td>
<td>318 (31.4%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>421 (41.4%)</td>
</tr>
<tr>
<td>Oral contraceptive (ever use)</td>
<td>440 (46.9%)</td>
</tr>
<tr>
<td>Sexually transmitted diseaseb</td>
<td>122 (12.0%)</td>
</tr>
</tbody>
</table>

aCombined cohort includes subjects from the Montreal General Hospital (n = 266), the Feinberg School of Medicine, Northwestern University, Chicago (n = 302) and the University of Birmingham, UK (n = 447). Missing data in 77 for OC use, and 13 for tobacco use.

bIncludes self-reported history of syphilis, gonorrhoea, chlamydia, herpes simplex and venereal warts in the Montreal and Chicago patients.

Table 2. Logistic regression analyses for the combined lupus cohort (1015 subjects); odds ratios (OR) of ever having an abnormal Pap smear report (134 cases), according to covariate factor

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually transmitted diseaseb</td>
<td>2.8 (1.8, 4.4)</td>
<td>2.5 (1.6, 4.1)</td>
</tr>
<tr>
<td>Oral contraceptive (ever use)</td>
<td>3.3 (2.2, 4.9)</td>
<td>2.9 (1.9, 4.4)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>0.9 (0.6, 1.3)</td>
<td>1.0 (0.7, 1.5)</td>
</tr>
<tr>
<td>Tobacco use (ever smoked)</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.9 (0.5, 1.3)</td>
</tr>
</tbody>
</table>

aAdjusted for all covariates listed in the table, as well as for age, race and centre.

bIncludes self-reported history of syphilis, gonorrhoea, chlamydia, herpes simplex and venereal warts in the Montreal and Chicago patients, and of herpes simplex in Birmingham.

Discussion

Previous work has suggested an association between SLE and cervical dysplasia [1–4] but the determinants of this association are not clear. The four studies that have previously examined exposure to immunosuppressive medication as a putative causative factor for cervical dysplasia in SLE were of small numbers of patients. Although these studies were unable to generate strong conclusions because of their limited sample size, in each there were trends towards more cases of dysplasia in patients exposed to immunosuppressives (cyclophosphamide, methotrexate and azathioprine).

Ours is the first attempt to examine the effect of a multitude of factors on the risk of abnormal Pap test results in SLE. Our previous work in the Montreal General Hospital sample had suggested that SLE patients may have a distinct prevalence profile for cancer risk factors with respect to several factors influencing the risk of cervical dysplasia and neoplasia, compared with the general population [5]. For example, nulliparity was 18% greater among the SLE sample, compared with age- and sex-adjusted population rates, and oral contraceptive use was 6% less (95% CIs excluded the null values). Smoking prevalence was similar. The profile of these factors (less use of OCs and more nulliparity) would tend to decrease the risk of cervical dysplasia and cancer. Other factors, such as exposure to immunosuppressive medication [3] appear to increase the risk.

The strengths of our study include the much larger sample size of an unselected group of women with SLE from several centres. Also, we performed adjusted analyses to quantify the risk associated with exposure to immunosuppressives, which has not been done before. We chose a questionnaire design in order to obtain information on covariates of interest, including STDs. Actual review of the Pap smear results of all of the subjects would not have been feasible.
for logistical reasons (including both cost and the fact that older specimens would not have been available). We do acknowledge that self-report of the frequency of abnormal Pap results is not perfect (a recent study found that 11% of women in a general population survey incorrectly stated that their last Pap test was normal [14]). Of course, self-report may be more accurate in our sample (which includes women with a chronic disease who are regularly followed by a physician). For example, we recently compared, in our Montreal lupus patients, the agreement between the self-report of cancers (all types) versus cancer registry records [15], and found a higher sensitivity of self-report compared with what has been published in the general population [16].

However, we would be remiss if we did not consider the possibility of information bias in our sample. One might expect there to be imperfect self-report (i.e. under-reporting) of history of STDs, for example, either because of recall error or hesitancy to admit to the fact. There may also have been some error introduced with respect to the data obtained from chart review on both exposure and outcome in the case of patients deceased or lost to follow-up. The question is whether this occurs non-differentially, or if it might occur differentially among women with a history of abnormal Pap tests. Whether women who have had an abnormal Pap test might be more likely to recall a history of symptomatic STDs is not known. However, many STDs are asymptomatic in women, and these infections would be more likely to be picked up in women who engage in regular contact with a gynecologist for cervical screening. Thus, some of the association between STDs and abnormal Pap tests which we found may reflect this bias. However, there remains strong biological plausibility (i.e. the association in the literature between certain STDs and cervical dysplasia) for the association that we demonstrated in terms of its direction and magnitude. Also, we note that for the self-report items examined, the direction and magnitude of the effects of these factors on history of abnormal Pap tests seems consistent with the literature in terms of their effects on cervical dysplasia.

Use of immunosuppressive agents may predispose lupus patients to infection (or delay the clearance of infectious agents) and thus allow viral and other infectious triggers to initiate abnormal cell differentiation, conferring malignant potential. Though HPV is the infectious agent most associated with cervical dysplasia and cancer [8], chlamydia has also been potentially implicated [9, 10]. Recent work has suggested that women with SLE have an increased prevalence of HPV infection [17]. Whether this is due to exposure to medication or a baseline abnormality in the immunology of patients with SLE [18] is unknown.

Recent guidelines published by the American College of Obstetricians and Gynecologists (ACOG) [19] suggest that yearly cytological screening should be performed in women younger than 30, and that older women who have had three consecutive negative cytologies for intraepithelial lesions or malignancy may be screened every 2–3 yr. However, because HPV infection and cervical dysplasia occur more frequently in HIV-infected women [20], the current recommendations are that all HIV-infected women should be screened at least annually for cervical cancer with Pap smears. The ACOG also extend this recommendation to women receiving immunosuppressive agents, which would include many women with SLE.

What is not clear is whether all women with SLE, regardless of exposure history, should be followed this closely (i.e. at least annually). Though our research does not address this issue, previous publications suggest high rates of cervical dysplasia even in women with SLE who are not on immunosuppressive medications [2]. Alternatively, the risk factors that we found to be associated with a history of lifetime abnormal Pap smear reports in our subjects (OC use and history of STDs) could serve as markers for those SLE patients likely to have a higher baseline risk of cervical dysplasia, regardless of immunosuppressive medication use. Unfortunately, the rheumatologist overseeing the long-term care of the SLE patient may not be aware of these history items, thus the high-risk patients may not be evident from that perspective.

In summary, although abnormal Pap test results in SLE appear in part to be influenced by the same factors that are important in the general population, exposure to immunosuppressives may confer further risk. Annual cytological screening should be performed in all SLE patients exposed to immunosuppressive agents, and prudence may suggest that all women with SLE follow this recommendation.

Acknowledgements

We thank Tina Panaritis (research assistant, Montreal General Hospital) as well as Stephanie Heaton RGN, Janet Skan BSc, and Veronica Toescu (Birmingham) for their assistance. In addition, we wish to acknowledge the following funding sources: the Birmingham lupus cohort is supported by LUPUS UK. Dr Bernatsky has received fellowship funding from the Canadian Institutes of Health Research (CIHR)/Lupus Canada, and the Canadian Arthritis Network; R. Ramsey-Goldman has received grants/research support from the following sources: Arthritis Foundation Clinical Science Grant, NIH AR 02138, NIH AR 48048; Lupus Foundation of Illinois. Dr A. Clarke has received the following funding: National Cancer Institute of Canada (NCIC) No 013135; the Arthritis Society No 99105; CIHR No 10005; Singer Family Fund for Lupus Research. Dr Joseph is a Senior Canadian Institutes of Health (CIHR) Investigator and Dr Rajan is a Fonds de la Recherche en Sante du Quebec (FRSQ) Clinician Scholar.

The authors have declared no conflicts of interest.

References


