The Association of Lichen Sclerosus and Erosive Lichen Planus of the Vulva With Autoimmune Disease

A Case-Control Study

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Objective: To investigate the prevalence of autoimmune disease and circulating autoantibodies in women with lichen sclerosus (LS) and erosive lichen planus (LP) of the vulva and to compare these with a control population.

Design: Age- and sex-matched controlled study.

Setting: The vulval clinics in Oxfordshire, England, for patients with LS and LP. Healthy controls were recruited from the hospital and community.

Patients: A total of 190 women with the typical features of adult-onset LS of the vulva, 126 women with adult-onset erosive LP of the vulva, and 922 female controls (of whom 230 were examined).

Interventions: Personal history of autoimmune disorder for patients and controls, family history of autoimmune disorder for vulval LS and LP cohorts, and an autoantibody screen.

Main Outcome Measures: The presence or absence of a personal or family history of autoimmune disorder, and the presence or absence of 1 or more circulating autoantibodies.

Results: The mean ages of patients with LS, patients with erosive LP, and control patients were 63, 61, and 61 years, respectively. The mean age of the 230 controls examined (including those who had serum autoantibodies assayed) was 62 years. Autoimmune disorders were more frequent in patients with erosive LP compared with controls (29% vs 9%; \(P < .001\)) and in those with LS compared with controls (28% vs 9%; \(P < .001\)). Circulating autoantibodies were more frequent in those with erosive LP compared with controls (41% vs 20%; \(P < .001\)).

Conclusion: This study demonstrates an association of autoimmune disorder and autoantibodies with erosive LP of the vulva and confirms the autoimmune associations of vulval LS.

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An autoimmune etiology has been proposed for lichen sclerosus (LS) because of an association with autoimmune disorders and circulating organ-specific antibodies. Antibodies targeting extracellular matrix 1 protein are present in 67% of the sera of patients with LS, and antibodies targeting the basement membrane zone (chiefly BP180 and BP230) are present in 30% of sera. The evidence for an increased association with other autoimmune disorders is thus far weak. One small controlled study compared the prevalence of autoimmune disorders and serum autoantibodies in 50 patients with LS and 50 healthy controls and found an increased prevalence of both autoimmune disorders and autoantibodies in those with LS. A larger study of 350 women with LS did not have a control group but reported a high prevalence of associated autoimmune disorders (21%). The most frequent autoimmune disorder was thyroid disease (12%). A prevalence of thyroid disease (30%) was found in a recent study of patients with LS. The prevalence of autoimmune disorders in patients with erosive lichen planus (LP) of the vulva is unknown. However, antibasement membrane zone antibodies chiefly targeting BP180 are present in 61% of erosive LP sera, suggesting that autoimmune mechanisms may be important in its pathogenesis.

The aim of this study was to investigate the prevalence of autoimmune disease and circulating autoantibodies in adult women with vulval LS and erosive LP of the vulva and to compare these with a control population.

See also pages 1502 and 1520

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A total of 190 women with the typical features of adult-onset LS of the vulva and 126 women with adult-onset erosive LP of the vulva (defined as onset postmenarche) were recruited from all women attending the dedicated vulval clinics in Oxfordshire, England. A control group of women were recruited as part of a study of postmenopausal women. All study and control patients were of North European ethnicity. Recruits for the control study were obtained from the community via 2 general practices in Oxfordshire and through posters displayed in the dermatology department and the breast cancer screening unit. Permission for these studies was given by the ethics committee (individual ethics submission codes CO2.118, CO2.290, and CO3.081). A questionnaire eliciting information on a personal history of autoimmune disease was completed by 922 women. Of these 922 women, 230 agreed to be examined (hereinafter, examined controls), and 112 underwent blood tests for serum autoantibodies detected in disease and control sera and for thyroid function assayed) was 62 years (range, 46-83 years; median age, 59 years) were very similar. The mean age of the 230 control patients examined (in- cluding those who had serum autoantibodies and thyroid function assayed) was 62 years (range, 46-83 years; median age, 60 years).

Results were taken as antibody titers above the upper limit of the clinically significant range. For thyroid peroxidase antibodies, this was defined as greater than 60 U. For antinuclear antibodies (Hep 2000 assay; Immuno Concepts, Sacramento, California), a titer of 1:80 or higher was deemed positive (titers of 1:80 were defined as weak antibodies).

The results of patients with LS and those with erosive LP of the vulva and control patients were compared using descriptive statistics. The \( \chi^2 \) test was used to compare the number of serum autoantibodies detected in disease and control sera and to compare the prevalence of personal history of autoimmune disorders. In the event of low expected cell counts, a Fisher exact test was performed.

The mean and median ages of the LS cohort (mean age, 63 years [range, 19-90 years]; median age, 64 years), erosive LP cohort (61 years [range, 29-85 years]; median age, 63 years), and normal control cohort (61 years [range, 39-94 years]; median age, 59 years) were very similar. The mean age of the 230 control patients examined (including those who had serum autoantibodies and thyroid function assayed) was 62 years (range, 46-83 years; median age, 60 years).

Fifty-four women (28%) with LS, 37 women (29%) with erosive LP of the vulva, and 80 controls (9%) (12% of examined controls) had 1 or more associated autoimmune disorders (Table 1). Associated autoimmune disorders were significantly more prevalent in the LS and LP cohorts compared with controls (\( P < .001 \) and examined controls (\( P < .001 \)). Thyroid disease was the most prevalent autoimmune disorder, occurring in 16% of the LS cohort, 15% of the erosive LP cohort, 8% of controls,
and 10% of examined and tested controls (among which 2 new cases of hypothyroidism were identified). Some individual autoimmune disorders were significantly more frequent in the LS cohort compared with controls, including thyroid (16% vs 8%; \( P < .001 \)), alopecia areata (3% vs 0.1%; \( P < .001 \)), pernicious anemia (4% vs 0.1%; \( P < .001 \)), and morphea (2% vs 0%; \( P = .01 \)). The autoimmune disorders that were significantly more prevalent in erosive LP were thyroid disease (15% vs 8%; \( P < .001 \)), alopecia areata (4% vs 0.1%; \( P < .001 \)), and celiac disease (2% vs 0.2%; \( P = .01 \)). One woman diagnosed as having erosive LP of the vulva had multiple autoimmune conditions, including vitiligo, Addison disease, premature menopause, hypogammaglobulinemia, thymoma, Sjögren disease, and chronic autoimmune urticaria, but did not meet the criteria for type 2 autoimmune polyendocrine syndrome.

The presence or absence of a family history of autoimmune disorder was obtained in 190 of 190 women in the LS cohort and 124 of 126 women in the LP cohort (Table 2). A total of 55 women in the LS cohort (29%) and 39 women in the LP cohort (31%) reported a family history of 1 or more autoimmune diseases in a first-degree relative.

Serum autoantibody assays were undertaken in 190 patients with LS, 126 patients with erosive LP, and 112 control patients. One or more serum antibodies were present in sera from 39 patients in the LS cohort (21%), 52 patients in the erosive LP cohort (41%), and 22 controls (20%) (Table 3). The prevalence of 1 or more autoantibodies in patients with LS compared with controls was not significant (21% vs 20%; \( P = .76 \)), but there was a significantly higher prevalence of autoantibodies in patients with erosive LP of the vulva compared with controls (41% vs 20%; \( P = .002 \)). The 2 autoantibodies that were significantly more prevalent in sera from patients with erosive LP than in control sera were antithyroid antibodies (19% vs 9%; \( P < .001 \)) and antinuclear antibodies (25% vs 9%; \( P < .001 \)).

To our knowledge, this study is the first to demonstrate that autoimmune disorders are more frequent in women with erosive LP compared with age- and sex-matched controls (29% vs 9%; \( P < .001 \)). This contrasts with cutaneous LP, which is not associated with autoimmune disorder.\(^7\) One unusual case of autoimmune hypogammaglobulinemia was detected in our erosive LP cohort. Hypogammaglobulinemia has been reported in association with vulval,\(^8\) oral,\(^9\) and cutaneous LP.\(^9,10\) Circulating autoantibodies occurred more frequently in women with erosive LP compared with controls (41% vs 20%; \( P < .001 \)). Antinuclear (25%) and antithyroid (19%) antibodies were the most frequent antibodies detected.

In addition, our data, from the first large controlled study, confirm the findings of previous studies that autoimmune disorders are more frequent in women with LS compared with controls (28% vs 9%; \( P < .001 \)). The prevalence of autoimmune disorders in our cohort (28%) is similar to that in previous studies (21%-34%).\(^1,2\) Surprisingly, there was no difference between the prevalence of circulating in antibodies in patients with LS and controls (21% vs 20%; \( P = .76 \)). Previous reports have detected circulating autoantibodies in 25%\(^1\) to 71%\(^2\) of patients with LS, but differences in antibody detection methods or patient selection may explain the variation. Circulating antibodies in patients with LS compared with controls were similar despite the increased prevalence of thyroid disease in the LS cohort compared with controls (16% vs 8%; \( P < .001 \)). The control group preva-

### Table 2. Family History of Autoimmunity for First-Degree Relatives

<table>
<thead>
<tr>
<th>Disease</th>
<th>Positive Family History, No. (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For LS (n = 190)</td>
<td>For LP (n = 124)</td>
</tr>
<tr>
<td>With at least 1 disease</td>
<td>55 (29)</td>
<td>39 (31)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>44 (23)</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>8 (4)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vitiigo</td>
<td>5 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>T1 DM</td>
<td>28 (10)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>8 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: LP, lichen planus; LS, lichen sclerosus; T1 DM, type 1 diabetes mellitus.

*Fisher exact test.

### Table 3. Autoantibodies Detected in Patients With Lichen Sclerosus (LS) and Erosive Lichen Planus (LP)

<table>
<thead>
<tr>
<th>Autoantibodies (Reference Range)</th>
<th>Positive Sera in Patients With LS, No./Total No. (%)</th>
<th>Positive Sera in Patients With Erosive LP, No./Total No. (%)</th>
<th>Controls, No. % (n = 112)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With at least 1 Ab</td>
<td>39/190 (21)</td>
<td>52/126 (41)</td>
<td>22 (20)</td>
<td>.76</td>
</tr>
<tr>
<td>Antithyroid Ab</td>
<td>17/190 (9)</td>
<td>24/126 (19)</td>
<td>10 (9)</td>
<td>.99</td>
</tr>
<tr>
<td>Antinuclear Ab (1:80)</td>
<td>19/181 (10)</td>
<td>23/126 (25)</td>
<td>10 (9)</td>
<td>.36</td>
</tr>
<tr>
<td>Anti–smooth muscle Ab (1:80)</td>
<td>4/181 (2)</td>
<td>4/22 (1)</td>
<td>1 (1)</td>
<td>.37*</td>
</tr>
<tr>
<td>Anti–gastric parietal Ab (1:80)</td>
<td>6/180 (3)</td>
<td>3/22 (3)</td>
<td>3 (3)</td>
<td>.53*</td>
</tr>
<tr>
<td>Antimitochondrial Ab (1:80)</td>
<td>1/179 (1)</td>
<td>2/22 (2)</td>
<td>1 (1)</td>
<td>.61b</td>
</tr>
</tbody>
</table>

Abbreviation: Ab, antibody.

*a* Nine of 10 had weak antinuclear antibodies (a titer of 1:80).

*Fisher exact test.

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lence of autoimmune thyroid disease (8%) is similar to that in a community survey of 1051 women (11.9%).
One possible explanation for the low detection of antibodies compared with clinical disease is that treatment of hypothyroidism with thyroxine may result in a decrease or disappearance of antithyroid antibodies.\(^{11}\) There were no significant differences between the prevalence of individual associated autoimmune disorders in the LS cohort compared with the erosive LP cohort (\(P\) values ranged from .10 to > .99; Table 1).

The information on family history may be unreliable because no confirmation of diagnoses was possible, and the data may be subject to recall bias. Nevertheless, the reported prevalence of first-degree relatives with 1 or more autoimmune disorders in patients with LS (29%) and those with erosive LP (31%) is similar to the reported prevalence in 2 previous LS studies (21%-36%).\(^{1,2}\) The positive family history suggests that inherited factors predisposing to autoimmune disorder may be important in these conditions.

It is important in a study of this kind that the age, sex, and ethnicity of the disease and control populations are similar, as in our study, because autoimmune disorders are more frequent in females and the prevalence increases with age.\(^{12}\) Similarly, the level of circulating organ-specific antibodies rises with age even in healthy elderly individuals.\(^{12}\) In this study, a smaller examined cohort of the control group gave very similar results to the larger control group.

This study has demonstrated an association of autoimmune disorders and autoantibodies with erosive LP of the vulva and confirmed the autoimmune associations of vulval LS. In LS and LP, there is a strong dermal inflammatory infiltrate comprised of T lymphocytes. In LS, a specific T-cell response to BP180, a structural protein of the basement membrane zone, has been demonstrated.\(^{13}\) Autoantibodies targeting the basement membrane zone have been identified in the sera of some patients with LS\(^{14}\) and LP,\(^{14}\) as have antibodies to extracellular matrix protein 1 in both conditions.\(^{1,15}\) These antibodies may have a transient or amplifying role in the pathogenesis of these conditions but are unlikely to be primarily pathogenic. It seems more likely that, as with autoimmune thyroid disease, LP and LS are T-cell-mediated diseases.\(^{16}\) These data suggest that autoimmune mechanisms may be important in the pathogenesis of LS and LP. This demonstration of an increased prevalence of autoimmune disease and a positive family history suggest that, in both these vulval disorders, there is a susceptibility to autoimmune disease supporting the concept that they are autoimmune disorders.

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Author Contributions: Dr Cooper had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Cooper, Ali, Baldo, and Wojnarowska. Acquisition of data: Cooper, Ali, Baldo, and Wojnarowska. Analysis and interpretation of data: Cooper, Ali, Baldo, and Wojnarowska. Drafting of the manuscript: Cooper and Wojnarowska. Critical revision of the manuscript for important intellectual content: Cooper, Ali, Baldo, and Wojnarowska. Statistical analysis: Cooper. Obtained funding: Wojnarowska. Administrative, technical, and material support: Cooper, Ali, and Baldo. Study supervision: Wojnarowska.

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REFERENCES