Influence of Treatment of Erosive Lichen Planus of the Vulva on Its Prognosis

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**Objective:** To record the clinical features, symptomatic response to treatment, and resolution of clinical signs in a large cohort of women with erosive lichen planus of the vulva.

**Design:** Descriptive, prospective cohort study with a mean follow-up of 72 months.

**Setting:** The vulval clinics of a teaching and district general hospital in Oxfordshire, England.

**Patients:** One hundred fourteen adult women with a definite clinical diagnosis of erosive lichen planus of the vulva.

**Interventions:** Patients received topical corticosteroids with or without other topical preparations and systemic treatments as part of their normal care.

**Main Outcome Measures:** Symptomatic response to individual treatments (good, partial, or poor), overall symptomatic response to treatment and with time (good, partial, no change, or worse), response of the vulval signs (total, partial, moderate, minor, same, or worse), and the presence or absence of moderate or severe scarring.

**Results:** The mean age at onset of vulval symptoms was 56.9 years. First-line therapy was an ultrapotent topical corticosteroid in 89 women (78%), of whom 63 (71%) were symptom free while receiving treatment. Overall and with time, 86 women (75%) improved with treatment, including 62 (54%) who were symptom free (good response) and 24 (21%) who had a partial response. Eighteen (16%) had no change and 10 (9%) were worse. Overall response of the vulval signs was recorded in 113 patients. Only 10 (9%) of these had complete resolution of clinical signs excepting scarring, with 57 (50%) showing resolution of erosions. Squamous cell carcinoma developed in 3 women (3%).

**Conclusions:** Topical ultrapotent corticosteroid is an effective treatment for erosive lichen planus of the vulva, giving relief of symptoms in 71%. With time and treatment, three quarters of patients can expect overall improvement of symptoms and one half, healing of erosions.

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EROSIVE LICHEN PLANUS OF THE vulva (ELPV) is a chronic inflammatory, scarring disease and a variant of classic lichen planus. It is characterized by painful vulval introital erosions, edged by a reticulate white border extending into the vagina. The presence of mucosal disease distinguishes lichen planus (LP) from lichen sclerosus, in which vaginal involvement almost never occurs. Scarring may result in marked architectural change with loss of the labia minora, clitoral burying, and narrowing of the introitus. In the presence of oral and vaginal disease, ELPV has been termed the vulvovaginal-gingival syndrome. However, not all patients have involvement of all 3 sites; some have vulval and vaginal disease without oral disease, vulval and oral disease without vaginal disease, or vulval disease alone.

The cause of erosive LP is unknown, although increasing evidence suggests that LP is a T-cell-mediated disease, representing an autoimmune response to altered self-antigens or heterogeneous foreign antigens. An association of oral and cutaneous LP with HLA-DR1 suggests a genetic component.

To date, there have been very few studies of vulval LP, and all have been retrospective. One of the largest and most complete clinical studies is the series by Eisen of 22 female patients with the vulvovaginal-gingival syndrome. Information on outcome and likely response to treatment is not available; thus, it has been difficult to give advice to patients with ELPV as to prognosis, likely response to treatment, and risk of vulval malignancy. To our knowledge, there are no randomized controlled trials of treatment of ELPV to date. For oral and cutaneous LP, systematic literature reviews have been unable to provide good evidence-based guidelines for treatment. In particular, no evidence has been cited of the efficacy of topical corticosteroids widely used as first-line treatment for cutaneous LP.
The aim of this study was to determine prospectively the clinical course of a large cohort of women with ELPV treated in a vulval clinic.

METHODS

PATIENTS AND DATA COLLECTION

We included a total of 114 women with the typical clinical features of ELPV. All patients attended 1 of 2 vulval clinics at a teaching hospital or a district general hospital in Oxfordshire, England, for a 5-year period. Some women had been diagnosed as having ELPV before the study commenced. The entry criterion for the study was a definite clinical diagnosis of ELPV. A vulval biopsy was performed if the patient gave consent, but the absence of vulval biopsy findings was not a contraindication to inclusion if there was no clinical doubt as to the diagnosis. Vulval histopathological findings were graded as diagnostic, probable (consistent with but not diagnostic), possible, and nondiagnostic. We excluded cases of overlap LP/lichen sclerosus. Fifteen women in this study have been previously described in a retrospective study of vulval LP.6

For all patients, we collected information by means of direct interview, clinical examination, and case note review by 1 physician (S.M.C.). Ethical permission to record data was obtained from the hospitals’ ethics committees. We collected demographic information, including age and racial origin. Anonymous patient data were entered into a database (Microsoft Access, version 2000; Microsoft Corp, Redmond, Wash) for analysis. All patients were seen as frequently as necessary until symptoms improved or stabilized and then every 6 months for review.

ONSET OF SYMPTOMS AND DIAGNOSIS

Age at onset was taken as the age when patients first experienced LP-related symptoms in the anogenital area. Age at diagnosis was defined as the age when a clinical diagnosis was established (usually the first visit to the dermatology clinic). The timing of disease onset (onset of symptoms) was grouped, in relation to menstrual history (including artificial menopause such as hysterectomy with bilateral oophorectomy), into premenopausal, perimenopausal (within 2 years before or after menopause), and postmenopausal onset. The delay in diagnosis was recorded as the time (in years) from the patient-reported onset of symptoms and definite diagnosis. The follow-up time (in months) from diagnosis was recorded. The age at onset of oral, vulval, and perianal symptoms was ascertained.

CLINICAL SYMPTOMS AND SIGNS

The presence or absence of vulval pain, pruritus, dyspareunia, urinary symptoms, perianal/bowel symptoms, vaginal discharge, and a history of pain or difficulty with cervical smear examinations was recorded before treatment. We noted the presence or absence of vulval clinical signs (erythema, pallor, atrophy [wrinkled skin and textural change], purpura, erosions, lacy white border, hyperkeratosis, and fissuring) and perianal signs (erythema, erosions, white reticulation, and hyperkeratosis). Oral pain or discomfort was noted, and the presence or absence of buccal reticulation, erosions, and desquamative gingivitis was recorded. Vaginal involvement and the presence or absence of vaginal disease was assessed by means of visual inspection (with or without speculum unless limited by pain or stenosis) or inspection at the time of vulval or vaginal biopsy (if performed under general anesthesia). The presence of LP in other sites (eg, scalp, nails, skin, ears, or esophagus) was determined by history, with examination and further tests performed if indicated.

VULVAL SCARRING

Vulval architectural change was graded as absent (no scarring), mild (minor fusion or minor labial adhesion and reduction), moderate (loss of labia and partial burying of the clitoris), or severe (complete loss of the labia, burying of the clitoris, and narrowing of the introitus).

RESPONSE TO TREATMENT

All treatments (surgical, systemic, and topical) given for ELPV were recorded. The potency of a topical corticosteroid applied during the initial treatment phase (usually 3 months) and for maintenance therapy was recorded. Efficacy of each individual treatment was recorded as good, partial, or poor from a combination of patients’ symptoms and clinical response. In addition, the overall symptomatic response to treatment(s) and time during the total review period was graded as good (symptom free during the treatment), partial (improvement and/or partial resolution of individual symptoms), no change, or worse. Response of the vulval physical signs to treatment was determined by comparing signs at definite diagnosis or on entry to the study with signs at the most recent visit to the vulval clinic. Response of ELPV was graded as total (complete resolution of the clinical signs with return to normal color and texture, with the exception of scarring), partial (lacy reticulation but no erosions or glazed erythema), moderate (glazed erythema but no erosions), minor (improved minor erosions), same (persistent widespread erosions), or worse (enlarging erosions). Overall symptomatic response and changes in the physical signs were assessed at the most recent review appointment after a minimum of 12 months of treatment.

STATISTICAL ANALYSIS

We examined the cohort using descriptive statistics. We used the χ² test to examine the strength of the association between the presence or absence of moderate or severe scarring and duration of symptoms for longer than 2 years before diagnosis.

RESULTS

ONSET OF SYMPTOMS AND SIGNS

All but 2 of the 114 women were of North European descent. Vulval biopsies were performed in 97 (85%), of which 75 results were graded as diagnostic or probable; 14, possible; and 7, nondiagnostic. One result was lost. The mean age at diagnosis was 62.1 years (range, 29-82 years), and the mean age at onset of self-reported vulval symptoms was 56.9 years (range, 27-79 years). Mean age at onset of oral symptoms (present in 50 women) was 55.5 years (range, 22-82 years), and of perianal symptoms (present in 23), 59.8 years (range, 40-78 years). The onset of vulval disease was premenopausal in 19 (17%), perimenopausal in 17 (15%), and postmenopausal in 78 (68%). Average length of follow-up after diagnosis was 72 months (range, 12-239 months).

CLINICAL SYMPTOMS AND SIGNS

The most frequently reported symptoms were vulval pain (91 [80%]) and pruritus (74 [65%]) (Table 1). The most
frequent signs at presentation were vulval erosions (111 [97%]) and white reticulations (94 [82%]) (Table 2). Signs of oral LP were observed in 67 patients (59%), perianal LP in 32 (28%), classic cutaneous LP in 22 (19%), and vaginal LP in 30 (58%) of the 52 patients fully examined. Other sites of involvement included the scalp in 9 patients (8%), nails in 4 (4%), esophagus in 2 (2%), external auditory meatus in 1 (1%), and lacrimal ducts in 1 (1%).

VULVAL SCARRING

One hundred eight women (95%) had some degree of vulval scarring, which was assessed as mild in 25 (22%), moderate in 53 (46%), and severe in 30 (26%). Delay in diagnosis of 2 years or more was not associated with more scarring (moderate or severe) at diagnosis ($P = .25$).

TOPOCAL CORTICOSTEROIDS

AND RESPONSE TO INDIVIDUAL TREATMENTS

The most frequent first-line treatment was an ultrapotent topical corticosteroid, 0.05% clobetasol propionate ointment, which led to symptomatic improvement in 84 (94%) of 89 women, with 63 (71%) being symptom free while receiving treatment (Table 3). A combined preparation (0.05% clobetasone butyrate, 3% oxytetracycline, and nystatin, 100 000 U/g [Trimovate]), was effective in 14 (100%) of 14 women, with 13 (93%) being symptom free while receiving treatment. The most frequent maintenance treatments were 0.05% clobetasol propionate ointment and a combined preparation, which were equally efficacious (good response in 17/25 [68%] and 32/50 [64%], respectively). No systemic treatments were consistently effective (Table 4). Seven women used topical tacrolimus with a mixed response. Twenty-one women (18%) underwent surgical treatment. Thirteen had surgical correction of introital stenosis (with a good response in 6, partial response in 3, and poor response in 4), 7 had division of vulval/vaginal adhesions (with a good response in 4, partial response in 1, and poor response in 2), and 1 had a partial vulvectomy with a poor response and recurrence of disease. Two women had surgical correction of introital stenosis twice, and 2 women had adhesions divided twice.

OVERALL RESPONSE TO TREATMENT

Overall response of reported symptoms (taken from the first visit to most recent review) to topical treatment was graded as symptom free in 62 patients (54%), partial response in 24 (21%), poor or no response in 18 (16%), and worse in 10 (9%). Vulval symptoms therefore improved in 75%.

Response of the physical signs (data available in 113 patients) was graded as total (complete resolution of the clinical signs with return to normal color and texture but without resolution of scarring) in 10 (9%), partial (lacy reticulation but no erosions or glazed erythema) in 12 (11%), moderate (glazed erythema but no erosions) in 35 (31%), minor (improved minor erosions) in 17 (15%), same (persistent widespread erosions) in 35 (31%), and worse (enlarging erosions) in 4 (4%). In 57 patients (50%), there was healing of erosions.

SQUAMOUS CELL CARCINOMA

AND VULVAL INTRAEPITHELIAL NEOPLASIA

Nine women developed vulval intraepithelial neoplasia (VIN) (7 patients) or squamous cell carcinoma (SCC) (3), including 1 who developed a vulval SCC on a background of previous VIN III. The first SCC arose in the oral cavity, the second in the perianal area, and the third on the labium minus. The mean age at onset of vulval symptoms was similar in the 3 women who developed SCC, the 7 women with VIN, and those with uncomplicated ELPV (61.0, 50.5, and 56.7 years, respectively) as was the mean age at diagnosis of LP (62.3, 59.3, and 61.4 years, respectively). The delay in diagnosis of LP in the SCC, VIN, and uncomplicated ELPV groups was 1.7, 8.8, and 4.7 years, respectively. Owing to the small number of tumors, the study had insufficient power to confirm a statistical difference between the 3 groups.
This study examined the clinical characteristics and response to treatment of a large cohort of patients with ELPV. It is the first prospective study to document the response of the clinical signs and symptoms of ELPV to treatment. This study confirms that ELPV is a disease of perimenopausal and postmenopausal women, with a mean age at onset of symptoms of 57 years, similar to findings of other series (age range, 49-52 years). In contrast, extragenital cutaneous LP has a younger age at onset, usually occurring in the fourth to sixth decades of life.

Achieving definite histological proof of LP in mucosal sites is very difficult compared with classic cutaneous LP. Thus, patients were included in this study if they had the typical features of ELPV but with nondiagnostic histological findings for LP if no alternative diagnosis was suggested by those histological findings.

It is clear that ELPV causes considerable morbidity with frequent vulval pain (80%), pruritus (65%), and disruption of sexual functioning (61%). No women in this cohort were asymptomatic at presentation, unlike women with vulval lichen sclerosus, who may be asymptomatic. We found some degree of vulval scarring in almost all women (95%) with ELPV, with 83 (73%) having moderate or severe scarring. Thus, ELPV is a destructive disease, and in some cases urinary outflow obstruction may occur owing to severe introital stenosis.

Some previous reports have suggested that the prognosis for ELPV is poor with difficulties in treatment, but this cohort showed a good response to treatment. Vulval symptoms improved in three quarters (75%) of the women with time and treatment and in approximately half (54%) who had become asymptomatic. In 50%, there was healing of vulval erosions. Despite good symptomatic response to treatment, the clinical signs of erosive disease tended to persist, with only 9% showing complete remission of clinical signs (with the exception of scarring) in contrast to vulval lichen sclerosus, with 23% showing complete remission with treatment.

Ultrapotent topical corticosteroids used twice daily for 3 months initially are our current first-line treatment for ELPV. This practice is justified by the finding that 71% of our patients were symptom free while receiving treatment. A combined preparation consisting of a corticosteroid and antifungal and antibacterial medications was as effective, with 93% of women with erosive disease becoming symptom free during use. This raises the possibility that a combined potent preparation may be as effective or more for initial treatment than a superpotent topical corticosteroid. Ultrapotent and combined preparations were also effective maintenance treatments (advised use as required), with symptoms improving in 24 (96%) of 25 and in 47 (94%) of 50 women, respectively.

### Table 3. Efficacy of First-line and Maintenance Topical Corticosteroid Treatments in ELPV

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>No. (%) Prescribed</th>
<th>Good</th>
<th>Partial</th>
<th>Poor</th>
<th>Response, No. (%)</th>
<th>No. (%) Prescribed</th>
<th>Good</th>
<th>Partial</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05% Clobutasol propionate ointment</td>
<td>89 (78)</td>
<td>63 (71)</td>
<td>21 (24)</td>
<td>5 (6)</td>
<td>25 (20)</td>
<td>17 (68)</td>
<td>7 (28)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Combined 0.05% clobetasone butyrate, 3% oxytetracycline, and nystatin, 100 000 U/g</td>
<td>14 (12)</td>
<td>13 (93)</td>
<td>1 (7)</td>
<td>0</td>
<td>50 (41)</td>
<td>32 (64)</td>
<td>15 (30)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>0.25% Beclometasone dipropionate</td>
<td>5 (4)</td>
<td>1 (20)</td>
<td>5 (40)</td>
<td>0</td>
<td>11 (9)</td>
<td>9 (82)</td>
<td>1 (9)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>0.1% Betamethasone ointment</td>
<td>3 (3)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>0</td>
<td>11 (9)</td>
<td>5 (45)</td>
<td>5 (45)</td>
<td>1 (9)</td>
<td></td>
</tr>
<tr>
<td>0.1% Mometasone furoate ointment</td>
<td>1 (1)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>6 (4)</td>
<td>3 (60)</td>
<td>1 (20)</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>1% Hydrocortisone</td>
<td>1 (1)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10% Hydrocortisone acetate foam</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Prednisolone enemas</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other low-potency corticosteroid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10 (8)</td>
<td>3 (30)</td>
<td>4 (40)</td>
<td>3 (30)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total, No.</td>
<td>114</td>
<td>80</td>
<td>29</td>
<td>6</td>
<td>122†</td>
<td>71</td>
<td>37</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ELPV, erosive lichen planus of the vulva.

*Percentages have been rounded and might not total 100.
†Some women used more than 1 maintenance treatment.

### Table 4. Efficacy of Second-line Systemic and Noncorticosteroid Topical Treatments for ELPV

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total No. of Patients</th>
<th>Response, No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical tacrolimus</td>
<td>7</td>
<td>Good 2, Partial 3, Poor 2</td>
</tr>
<tr>
<td>Topical pimecrolimus</td>
<td>1</td>
<td>Good 0, Partial 1, Poor 0</td>
</tr>
<tr>
<td>Minocycline hydrochloride</td>
<td>6</td>
<td>Good 2, Partial 2, Poor 2</td>
</tr>
<tr>
<td>Erythromycin ethyl succinate</td>
<td>6</td>
<td>Good 3, Partial 2, Poor 1</td>
</tr>
<tr>
<td>Combined minocycline hydrochloride and niacinamide</td>
<td>5</td>
<td>Good 0, Partial 1, Poor 4</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>3</td>
<td>Good 1, Partial 1, Poor 1</td>
</tr>
<tr>
<td>Acitretin</td>
<td>4</td>
<td>Good 0, Partial 4, Poor 0</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2</td>
<td>Good 0, Partial 2, Poor 0</td>
</tr>
<tr>
<td>Azathioprine sodium</td>
<td>2</td>
<td>Good 0, Partial 1, Poor 1</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate</td>
<td>2</td>
<td>Good 0, Partial 2, Poor 0</td>
</tr>
<tr>
<td>Thiadizolidine</td>
<td>1</td>
<td>Good 0, Partial 1, Poor 0</td>
</tr>
<tr>
<td>Colchicine</td>
<td>1</td>
<td>Good 0, Partial 0, Poor 1</td>
</tr>
</tbody>
</table>

Abbreviation: ELPV, erosive lichen planus of the vulva.
Systemic treatments were surprisingly unhelpful, with a uniformly poor response to the systemic immunosuppressants methotrexate, cyclosporine, and azathioprine. Response to hydroxychloroquine sulfate was poor in contrast to the experience of others.\textsuperscript{13} The antibiotics erythromycin ethyl succinate, minocycline hydrochloride, and a combination of minocycline and niacinamide were helpful in some cases. The rationale for their use comes from their efficacy in the subepidermal autoimmune blistering disorders bullous pemphigoid, mucous membrane pemphigoid, and linear IgA disease,\textsuperscript{14-17} which have some phenotypic similarities to ELPV. Their mode of action is probably anti-inflammatory rather than antimicrobial.\textsuperscript{18} The reason for the poor response to systemic therapy (with the exception of antibiotics) is uncertain. One possible explanation is that systemic therapy was only commenced if there was an inadequate response to topical treatment, and thus those receiving systemic therapy may have had more severe disease and were less likely to respond. Other authors may have used systemic immunosuppression at an earlier stage or in those with less severe disease.

During the study period, reports were published regarding the efficacy of the topical calcineurin inhibitors tacrolimus\textsuperscript{19-21} and, in oral disease, pimecrolimus,\textsuperscript{22,23} and thus some women with resistant disease in this cohort started treatment. Two women with severe disease responded well to treatment, 1 with complete clearance of erosions after 10 years of active disease, but the response was less favorable in 5 others. It is possible that topical calcineurin inhibitors such as tacrolimus may play a role in treatment in the future, with the advantage of reduced skin atrophy compared with topical corticosteroids. A theoretical disadvantage is an increased risk of malignant transformation due to local immunosuppression. A comparative study between topical calcineurin inhibitors and topical corticosteroids for the treatment of erosive LP will be necessary.

Erosive LP of the vulva was frequently associated with LP at other mucosal or cutaneous sites. The prevalence of oral disease (59%) is similar to that in previous reports of vulval LP (53%-73%),\textsuperscript{2,4,24} except for patient series recruited from oral clinics with 100% oral involvement.\textsuperscript{8} The overall prevalence of vaginal disease (26%), but 58% of the 52 examined, is lower in this study than in some other series (58%-100%).\textsuperscript{25}; however, patients in these series were selected to illustrate the vulvovaginal-gingival syndrome and so are biased in favor of vaginal disease.\textsuperscript{3,25} One of the difficulties with the present study is that it proved impossible to examine the vagina adequately in all patients because of pain or narrowing of the introitus. Therefore it is likely that some cases of vaginal disease were missed. The frequency of nongenital cutaneous involvement (21% [24 patients in this study]) is similar to that in other studies (9%-20%).\textsuperscript{26} Esophageal LP is rare but well documented,\textsuperscript{27} but to our knowledge, only 1 case of external auditory meatus involvement has been reported previously.\textsuperscript{28}

Three patients developed SCCs (1 oral and 2 anogenital), giving a prevalence of 3% in the adult study population during a mean follow-up period of 72 months. In a similar study from our group of a large cohort with vulval lichen sclerosus, a prevalence of SCC of 2.4% was ascertained with a mean follow-up of 69 months.\textsuperscript{22} There are at least 12 reports of SCC and vulval LP, but no estimates of SCC risk.\textsuperscript{29-35} A much larger multicenter, longitudinal study will be necessary to evaluate accurately the characteristics of those who develop SCCs. It is unknown whether early treatment of LP lessens the risk of malignancy. There was a trend toward earlier presentation in the SCC group; however, this did not reach statistical significance owing to small numbers. It is possible that those who develop SCC may have more severe symptoms and present earlier.

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Author Contributions: Study concept and design: Cooper and Wojnarowska. Acquisition of data: Cooper. Analysis and interpretation of data: Cooper. Drafting of the manuscript: Cooper. Statistical analysis: Cooper. Study supervision: Wojnarowska. Dr Cooper had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


