

Vulvar Lichen Sclerosus

Effect of Long-term Topical Application of a Potent Steroid on the Course of the Disease

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Background: Lichen sclerosus is an inflammatory disease of unknown etiology affecting the anogenital skin and associated with the development of squamous cell carcinoma. It is not known whether long-term topical treatment with a potent steroid can cure this disease and thus prevent malignant evolution.

Objectives: To analyze the rates of remission, recurrence, and chronic evolution of vulvar lichen sclerosus (VLS) treated with 0.05% clobetasol propionate ointment and determine whether this treatment can decrease the risk of malignant evolution.

Design: Prospective study, conducted between 1981 and 2001, of 83 women with VLS who were treated until complete clinical and histologic remission and followed up for evidence of clinical and histologic recurrence (median follow-up, 4.7 years).

Setting: Dermatology department of a large urban teaching hospital.

Results: Complete remission was obtained in 45 patients (54%). The probability of remission was sig-

nificantly associated with age ($P < .001$). The estimated incidence of remission at 3 years was 72% in women younger than 50 years, 23% in women aged between 50 and 70 years, and 0% in women older than 70 years. The incidence of relapse was estimated to be 50% at 16 months (95% confidence interval, 30%-64%) and 84% at 4 years (95% confidence interval, 57%-94%). Age had no effect on relapse prevalence. The 8 observed vulvar squamous cell carcinomas (9.6%) occurred in previously untreated or irregularly treated VLS lesions.

Conclusions: Treatment with a potent steroid cream can improve but does not cure VLS in women older than 70 years, probably because of a long disease evolution. In younger patients who achieve complete remission, it seems to have only a temporary effect. Although a protective effect from malignant evolution is suggested (carcinoma developed only in nontreated or irregularly treated VLS lesions), the number of seemingly protected patients was too small to be statistically significant.

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LICHEN SCLEROSUS (LS) IS AN inflammatory disease of unknown cause that may be localized anywhere on the skin, but has a predilection for the genital area (vulva and penis). It affects men and women in a ratio estimated between 10:1 and 5:1; and although

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disease onset has been reported at all ages, it occurs most commonly in women in their fifth or sixth decade of life. The true incidence of genital LS is unknown because the condition is often undiagnosed. Several studies¹⁻⁶ have shown an association between genital LS and the risk of developing vulvar or penile squamous cell carcinoma (SCC).

The accepted treatment for genital LS is now 0.05% clobetasol propionate. It was reported to be more efficient than 2% progesterone ointment and 2% topical testosterone, which have been widely used in the past.⁷⁻⁹ Some studies suggest that potent corticosteroids have excellent long-term tolerance with minimal side effects in adults and children with genital LS.^{7,10-14} However, these studies only report on a treatment course of 3 months,^{7-10,12-14} and in those reporting on a 1-year follow-up, recurrences were common and required additional topical steroid treatment.^{9,10,12,14} All authors agree that genital LS runs a chronic course and in some cases does not remit. Because of the risk of malignant transformation, long-term follow-up is necessary.

No study has evaluated the effect of long-term use of a potent topical steroid

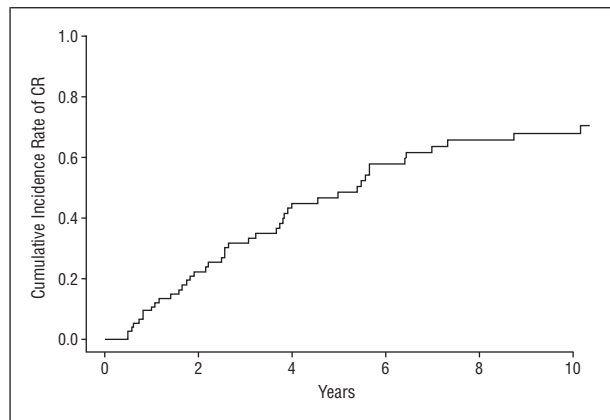


Figure 1. Cumulative incidence rate of complete remission (CR) for the whole cohort.

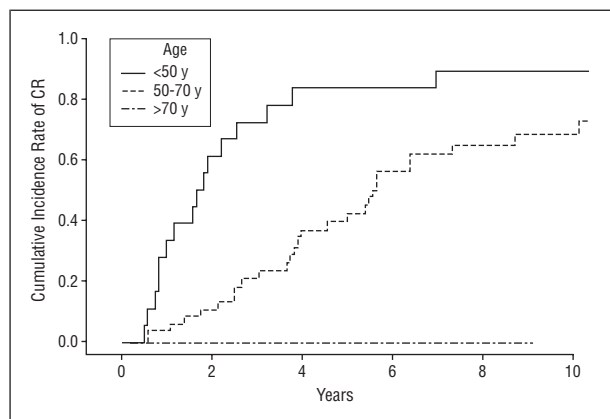


Figure 2. Cumulative incidence rate of complete remission (CR) according to global effect of age at inclusion ($P < .001$; Gray test).

on the course of the disease, ie, determined whether cure or remission can be obtained and, if so, the rate of recurrence after ending the treatment. Another question is still a matter of conjecture: could long-term treatment prevent malignant transformation?

The purpose of this study was to evaluate the effect of long-term application of a potent topical steroid cream on the course of vulvar LS (VLS) by analyzing the rates of complete remission (CR), recurrence, and chronic course (ie, course without CR), as well as the potential role of this treatment on malignant transformation.

METHODS

We performed a prospective study of 83 women aged 20 years and older who had VLS and attended the vulvar clinic of the Hôpital Saint-Louis Department of Dermatology, Paris, France, between January 1981 and June 2001. The lesions had to be confirmed histologically and were not to have been previously treated. The histologic features of VLS were defined by a band of hyalinized collagen below an epithelium underscored by a bandlike lymphocytic infiltrate with decreased numbers of elastic fibers. The women were treated with 0.05% clobetasol propionate ointment, once daily for 3 months and then 3 times per week until CR. Complete remission was defined clinically as an absence of clinical signs of VLS (ie, no pruritus and a regression of white and sclerotic lesions), and histologically as the disappearance of the infiltrate and hyalinized collagen in

the dermis (with the persistence of a slight, mostly subepidermal fibrosis) with some improvement of the elastic network. Complete remission was used instead of cure because of the possibility of relapse. The treatment was ended only when CR was obtained. In the absence of remission after 12 to 18 months, the frequency of applications was gradually tapered to twice per week. Follow-up visits were scheduled every 3 months for the first 6 months and then twice per year. During follow-up, relapses were defined clinically as new VLS lesions (areas of pallor with or without pruritus or pain), and histologically when histologic examination showed the reappearance of hyalinized foci of collagen with decreased numbers of elastic fibers with or without lymphocyte infiltrate.

A competing risks analysis of time to CR was performed using cumulative incidence curves, with death as the competing event. The effect of age as a prognostic factor of remission was then assessed using the Gray test¹⁵ and the proportional subdistribution hazards regression model of Fine and Gray.¹⁶ The variable was first included as a continuous variable and then categorized into 5 classes of equal sample size according to its empirical distribution. Adjacent classes were subsequently grouped if their hazard ratios in the model were similar using the method proposed by Peto et al.¹⁷ A similar method was applied to the time to relapse in the subset of patients who experienced remission. However, as in the sample, no deaths occurred in the subset after remission and a classic method combining Kaplan-Meier-based cumulative incidence curves and Cox proportional hazards regression model was used. The effects of age and time to remission (representing treatment duration for compliant patients) as prognostic factors of relapse were analyzed. All tests were 2-sided, with a type I error rate fixed at .05.

RESULTS

The 83 patients' mean age was 59.4 years (range, 30-92 years) and the median follow-up time was 4.7 years (range, 2 months-19 years); 4 patients were lost to follow-up. In all cases the symptoms (eg, pruritus) regressed during the first 3 months of treatment. Complete remission was obtained in 45 patients (54%) (**Figure 1**). The cumulative incidence rate of CR was 32% at 3 years (95% confidence interval [CI], 20%-43%) and 58% at 6 years (95% CI, 45%-70%). A significant effect of age on the probability of CR was found ($P < .001$) (**Figure 2** and the **Table**). The estimated cumulative incidence rate of CR at 3 years was 72% in patients younger than 50 years and 23% in patients between 50 and 70 years; no patient older than 70 years reached CR.

The cumulative incidence rate of relapse after ending treatment was estimated at 50% at 1 year 4 months (95% CI, 30%-64%) and at 84% at 4 years (95% CI, 57%-94%) (**Figure 3**). No effect of age on relapse was found.

In 2 cases, treatment was interrupted for 1 month because of local inflammation due to steroid application, and then resumed; no case of contact sensitivity to clobetasol propionate was observed. There was only 1 case of genital candidosis in a patient with diabetes mellitus, which suggested that a potent topical steroid could—however rarely—contribute to infection. No systemic or local atrophic effects were observed.

Eight SCCs (9.6% of all cases) were observed, in 8 patients whose mean age was 68.6 years. Of these patients, 6 had carcinomas at first presentation and the associated VLS had never been treated before the occur-

Effect of Age on Probability of Complete Remission

Age, y	No. of Patients	Hazard Ratio (95% Confidence Interval)	P Value	Cumulative Incidence Rate at 3 y, %	Global P Value
<50	18	3.20 (1.63-6.30)	<.001	72.3	<.001
50-70	53	1*		22.7	
>70	13	3.33×10^{-5} (1.5×10^{-5} - 7.4×10^{-5})	<.001	0	

*Reference category.

rence of the tumor. In 1 woman who did not have follow-up, SCC occurred within 3 years of the end of treatment, and a microinvasive SCC developed in another woman who did not apply her treatment regularly, apparently because of severe depression. No significant effect of treatment duration on time to relapse was found.

COMMENT

The use of a potent topical corticosteroid in the treatment of genital LS is now commonly recognized as effective, with minimal adverse effects.⁷⁻¹⁴ Comparative studies^{7,8} have confirmed the greater efficacy of this medication compared with others, eg, 2% topical testosterone. The latter treatment, which was widely used in the past, now seems to have been a placebo producing only transient effects on symptoms^{7,18} but often associated with hyperandrogenism. The present study confirmed the efficacy of treatment with 0.05% clobetasol ointment and its good tolerance even with long-term application. The absence of an atrophic effect of the medication is surprising, but could be explained by the rapid decrease in application regimen with VLS improvement (to 3 times per week), and by the fact that most treated lesions were on the mucosa rather than the skin. A different susceptibility to long-term topical corticosteroid therapy between mucosa and skin could explain the differences in induced atrophy, but further studies are needed.¹⁹ Complete remission was obtained in 54% of cases, with a median follow-up of 4.7 years. Although some patients reached CR only after 6 years, the cumulative incidence curve of CR seems to plateau after this time (Figure 1), possibly indicating a chronic evolution of the disease. At 6 years, the possibility of CR was estimated at 58% and the probability of death before CR at 7%; from these estimations, we could estimate the probability of chronic evolution at 35% in the cohort. Interestingly, no remission was obtained in women older than 70 years. The younger the women, the higher their chance of CR (hazard ratio, 1.72/10 years). The failure of a potent topical steroid to induce VLS remission in previously untreated women older than 70 years could be due to disease duration, which might lead to irreversible changes.¹³ However, when remission occurs in younger women, treatment seems to have only a temporary effect since there were very frequent recurrences among them (the estimated rate was 84% at 4 years, and increased with follow-up duration). Recurrences after the end of initial treatment have been reported^{7,10} during follow-up in several studies. In these studies, treatment with 0.05% clobetasol

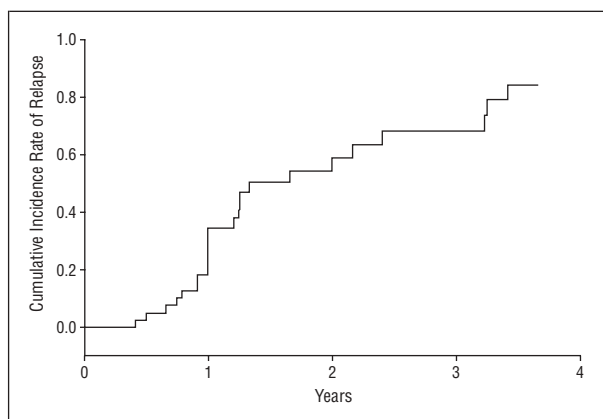


Figure 3. Cumulative incidence rate of time to relapse after complete remission.

propionate ointment lasted only 3 months and was terminated in the absence of confirmed CR. In our series long-term follow-up confirmed a high rate of relapses (84% at 4 years), even after long-term treatment and complete histologic remission.

The association between genital SCC and genital LS is well known. On the vulva, this risk has been evaluated at 4% to 5%.¹ Conversely, studies of tissue alterations adjacent to invasive vulvar SCC found evidence of LS in 61% to 76.1% of excised specimens.^{2,4,5} Carli et al³ reported a cumulative risk of vulvar SCC of 14.8% in a VLS cohort (vs 0.06% in the general female population), with a relative risk of 246.6. In this prospective study the risk of developing vulvar SCC for women having VLS is more than 300-fold that of unaffected women of similar age.

The protective effect of VLS treatment with 0.05% clobetasol propionate ointment on vulvar cancer development is still controversial. In a series of vulvar SCCs it was noted that none of the women with VLS had been treated before the occurrence of the carcinoma.⁴ In the series of Bornstein et al⁷ vulvar SCC developed in 1 woman who applied clobetasol during only 1 year and did not return for follow-up; carcinoma was diagnosed 3 years later. Carli et al³ reported vulvar carcinomas in 3 women treated for VLS, of whom only 2 had steroid applications. Lesions in these 2 women initially had histologic features of squamous hyperplasia (with atypia or differentiated vulvar intraepithelial neoplasia in 1 case), but only a short course of topical steroid (≤ 6 months) was prescribed during a follow-up of 3 to 4 years. Therefore, it is not possible to conclude that, in these reported cases, VLS treatment with a potent topical ste-

roid failed to prevent malignant evolution. In the present study, vulvar SCC was observed in 8 women (9.6% of cases), but 6 of them presented with a tumor at the initial visit and their associated VLS had never been treated. Another woman had discontinued treatment 3 years previously, had no follow-up, and returned to the clinic with a vulvar SCC on active VLS lesions. The last one had not applied the medication regularly because of a severe depressive illness. Thus, the other cases can suggest a protective effect of a potent topical steroid on VLS but the number of patients is too small to be significant. Interestingly, there is a difference of nearly a decade between the mean age of all the patients with VLS and those with vulvar carcinoma, which suggests that carcinoma occurred in long-standing lesions possibly associated with irreversible changes. Topical tacrolimus has recently been reported to be successful in the treatment of VLS, but further studies are needed to appreciate long-term efficacy and the possible adverse effects of this treatment.²⁰

CONCLUSIONS

Use of a potent topical steroid is still considered to be the most effective treatment of genital LS but it did not achieve CR of VLS lesions in women older than 70 years in this series. Chronic disease without effective treatment may lead to irreversible changes. The difference of a decade between the mean age of patients with VLS and patients with VLS plus malignant lesions indicates that transformation occurs preferentially in long-standing VLS lesions. In younger patients, even if remission can be obtained, recurrences are common. Thus, the treatment seems to have only a temporary effect on these patients; however, a protective effect from malignant evolution can be suggested because carcinoma occurred, in this series, only in untreated or irregularly treated VLS lesions. Thus, long-term steroid application could be useful in older women (even if no cure is obtained) to protect them from malignant transformation, and in younger women because of the temporary effect of this treatment, and because of the possibility of malignant change in untreated disease. Thus, we propose the following treatment schedule to our patients: 1 application per day of 0.05% clobetasol propionate ointment during the first 3 months, then 3 times per week until remission. In women with chronic evolution we are still studying the efficacy and possible adverse effects (eg, atrophy) of 1 application per week. However, in all cases, lifelong follow-up is necessary. We will follow up this group of women indefinitely to report on the evolution of their condition.

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