CED
Clinical and Experimental Dermatology

Mucosal (oral and vulval) lichen planus in women: are angiotensin-converting enzyme inhibitors protective, and beta-blockers and non-steroidal anti-inflammatory drugs associated with the condition?

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doi:10.1111/j.1365-2230.2009.03581.x

Summary

Aim. To determine whether there is an association between the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and nonsteroidal anti-inflammatory drugs (NSAIDS) in women with mucosal (oral and vulval) lichen planus (LP) compared with a control population.

Methods. This was a retrospective review of medical records in dedicated vulval and oral clinics in hospitals. The study population comprised 141 women with vulval LP and 106 women with oral LP. Medications taken at the time of diagnosis were recorded.

Results. Patients with mucosal LP were more likely to be on NSAIDS and beta-blockers, but less likely to be on ACE inhibitors compared with controls. All three groups were found to have an inverse relationship with ACE inhibitors, but no association was found between patients with oral LP and beta-blockers.

Conclusions. Beta-blockers and NSAIDS are associated with LP, suggesting that withdrawal of these drugs should be considered. Further studies are needed to confirm or refute the inverse relationship between mucosal LP and use of ACE inhibitors.

Introduction

Lichen planus (LP) is an inflammatory disorder that can involve the skin, oral and genital mucous membranes, scalp, and nails. LP is considered idiopathic, but there are anecdotal reports of various medications being associated. These include β-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), methyldopa, penicillamine, quinidine, quinine and angiotensin-converting enzyme (ACE) inhibitors.

LP is a relatively common disorder. Mucosal lesions include oral and genital lesions and are less common in men. Oral lesions occur as the only symptom of LP in 15–35% of patients but up to 65% of patients with classic cutaneous disease have oral involvement.[1] There are very few studies in the literature assessing the prevalence of vulval LP, but it is probably more common than previously thought. An Italian study found a prevalence of 3.7% in a dedicated vulval clinic[2] and Lewis *et al.* reported that in a group of 37 women with cutaneous LP, 51% had vulval lesions.[3]

There are several studies in the literature assessing the link between oral LP and medication usage,[4,5] but to our knowledge there have been no studies that include patients with vulval LP.

Drug-induced LP and idiopathic LP can be differentiated only by the time course of skin or mucous membrane involvement in relation to the drug and confirmed by rechallenge. Considering the variability in the disorder's natural history, diagnosing drug-induced LP can be difficult and a definitive diagnosis is generally

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Conflict of interest: none declared.

Accepted for publication 23 April 2009

not possible. There remains confusion in the oral mucosal literature regarding the disease nomenclature, where the term 'lichenoid reaction' is described, especially in cases with clinically atypical lesions, but this distinction is not made in vulval disease.

The aim of this study was to determine whether there is an association between mucosal (oral and vulval) LP in women using ACE inhibitors, beta-blockers and NSAIDS compared with a control population.

Methods

Permission for these studies was given by the ethics committee (CO2.118, CO2290), and all participants gave informed consent.

Participants

The patients were recruited from dedicated vulval and oral clinics with a definite clinical diagnosis of vulval LP and/or oral LP. The case records of 141 women with vulval LP (of which 128 had erosive disease) and 106 women with oral LP (of which 100 had erosive disease) were reviewed, and the medications taken at the time of diagnosis were recorded. For the purpose of this study, LP was defined as a typical clinical picture with supportive histology (when biopsy possible). Histology confirmed the diagnosis of vulval LP in 117 (83%) cases; the remaining 24 patients did not have a biopsy taken, because it was contraindicated or they declined. All patients with oral LP had a biopsy taken, which was histologically consistent with LP.

The control population was recruited from the community via two Oxfordshire general practices and patients, relatives and friends of patients attending the dermatology department and the breast-screening unit. They were recruited as part of a study examining the factors affecting hair growth in a normal population of postmenopausal women. All were of northern European ethnicity. A questionnaire eliciting information on medications was completed by 974 women, who were enrolled in the study.

The 141 women with vulval LP had a mean age of onset of 63 years (range 29–95), of whom 69 (49%) also had oral involvement. The 106 patients with oral LP had a mean age of onset of 56 years (range 24–86), of whom 17 (16%) had vulval involvement. The control population of 974 women recruited from the community had a mean age of 67 years (range 34–99). There was no significant difference in age between the groups ($P \leq 1.0$).

Statisitical analysis

The χ^2 test was used to examine the strength of the association between the presence or absence of individual medications in both the vulval and oral LP and control groups. $P \leq 0.05$ was considered significant.

Results

Drug associations

There was a significant difference between the number of patients with mucosal LP and controls on NSAIDs [36/247 (15%) vs. 36/974 (4%), $P = 0.001$] and beta-blockers [43/247 (17%) vs. 97/974 (10%), $P = 0.01$]. There was an inverse relationship between the presence of mucosal LP and use of ACE inhibitors ($P = 0.01$) (Table 1).

There were differences between individual sites. Vulval LP (whether as a sole site or in conjunction with oral LP) was associated with NSAIDs [12/158 (8%) vs. 36/974 (4%), $P = 0.03$] and beta-blockers [24/158 (15%) vs. 97/974 (10%), $P = 0.05$], and again, there was an inverse relationship between the presence of vulval LP and use of ACE inhibitors ($P = 0.03$) (Table 1). In contrast, oral LP (whether as a sole site or in conjunction with vulval LP) was associated with NSAIDs [24/175 (14%) vs. 36/974 (4%), $P < 0.001$], but not with beta-blockers. There was an inverse relationship with ACE inhibitors ($P = 0.001$) (Table 1).

Discussion

This study is the first to identify an association of medications with susceptibility to vulval LP and to compare the different mucosal sites. In addition, we have shown a potential protective effect of a drug on this condition.

The association of oral LP with a wide range of drugs has been appreciated for a considerable time[4,5] but to our knowledge, vulval LP has never been included in any series.

ACE inhibitors

From these data, ACE inhibitors seem to protect patients from developing mucosal LP (either oral or vulval). In all of our groups, fewer patients than controls were taking ACE inhibitors. This is surprising as there are many reports in the literature linking these medications with LP.[6–9] Potts *et al.*[4] also reported an inverse relationship between oral LP and antihypertensive

Table 1 Drug characteristics of controls and of patients with mucosal, vulval and oral LP.

		Patients					
	Controls	Mucosal LP	*P**	Vulval LP	*P**	Oral LP	*P**
Patients, *n*	974	247		158		175	
Drugs used							
NSAIDs, *n* (%)	36 (4)	36 (15)	≤ 0.001	12 (8)	≤ 0.03	24 (14)	< 0.001
Beta-blockers, *n* (%)	97 (10)	43 (17)	≤ 0.01	24 (15)	≤ 0.05	19 (11)	NS
ACE inhibitors, *n* (%)	120 (12)	14 (6)	≤ 0.01	9 (6)	≤ 0.03	5 (3)	< 0.001

ACE, angiotensin-converting enzyme; LP, lichen planus; NSAID, nonsteroidal anti-inflammatory drug; NS, not significant. *Compared with controls.

medications, although they did not specify the drugs (captopril and enalapril were in use at the time of publication).

Previously it has been shown that ACE inhibitors are capable of suppressing the production of monocytes/macrophage-derived proinflammatory cytokines such as tumour necrosis factor-α, interferon-α, interleukin (IL)-1, IL-6 and IL-12.[10–12] It is known that LP is characterized by a T-cell inflammatory infiltrate in the dermis and epidermis, and these activated T cells and keratinocytes have been shown to elicit T-helper (Th)1 and Th2 responses. It is possible that the ACE inhibitors have a direct inhibitory effect on activated T cells or an indirect effect, perhaps through antigen-presenting cells or regulatory T cells.

NSAIDs

We have confirmed the previously published association between NSAIDs and oral LP[5] and have shown that the association is also significant in vulval LP.

Potts *et al.*[4] found a significantly greater use of NSAIDs in patients with oral LP than in controls ($P < 0.03$); 17% of their LP patients were taking NSAIDs. Robertson and Wray[5] found that ingestion of NSAIDs was nearly 10 times more prevalent among those with erosions than in those with nonerosive LP ($P = 0.01$). Both papers suggest that as NSAIDs are known to produce mucosal ulceration in other parts of the gastrointestinal tract, they may therefore cause erosions at other mucosal sites. Most of our patients had mucosal erosions.

Beta-blockers

We have shown that beta-blockers may have a site-specific effect in patients with vulval LP. This association was not found in patients with oral LP. One proposed mechanism of action relies on the fact that there are β2 receptors broadly present in the skin. Cyclic adenosine monophosphate (c-AMP) is an intracellular messenger that stimulates proteins and is responsible for keratinocyte differentiation and inhibition of its proliferation. Beta-blockers are known to block c-AMP levels, therefore reduced c-AMP levels results in upregulation of keratinocyte proliferation, reduced differentiation and increased lymphocyte motility.

Conclusion

Our results shown an association of LP with beta-blockers and NSAIDs, suggesting that withdrawal of these drugs should be considered in such patients. Further studies are needed to confirm or refute the inverse relationship between mucosal LP and ACE inhibitor usage. Recent advice from the British Hypertension Society[13] has favoured a shift from beta-blockers to ACE inhibitors for the treatment of hypertension. A study assessing the effect of this change in medication in patients with mucosal LP would be important as it might lead to an improvement in the management of this intractable condition.

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