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Case Report

Low-Concentration Topical Tacrolimus Ointment in the Treatment of Vulvar Lichen Sclerosus in a Child

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Abstract

Observations: Lichen sclerosus is a chronic inflammatory disease with a predisposition of the anogenital region. Topical corticosteroid is effective; however, a continuous treatment is often required. After its stoppage the recurrence is often and the side effects of repeated local application of potent glucocorticosteroids may be seen that is why an equally-effective, safer therapeutic options are needed, especially in the treatment of children.

Here, we report a case of vulvar lichen sclerosus in a 6-year-old girl refracted to topical steroid. After 12 weeks of treatment with 0.03% tacrolimus ointment once daily, the lesions get resolved without any side-effects. This is our first case of topical tacrolimus treatment showing a dramatic effect in the treatment of childhood vulvar lichen sclerosus.

Introduction

Lichen sclerosus (lichen sclerosus et atrophicus: LS) was first described by *Hallopeau* in 1887 and its typical histology defined by *Darier* in 1892. The lesions are ivory-white papules and plaques, often showing central delling, atrophy, teleangiectatic speckling and purpura [1].

Lichen sclerosus is most common in postmenopausal women however it has another peak in prepubertal girls. Childhood LS represents 15% of total cases of the disorder, with a 10:1 ratio of females to males. In one review study on pediatric vulvar LS it was indicated a prevalence of 1:900 girls, with a mean age at symptom onset of 5.0 years but a mean age at diagnosis of 6.7 years. Although the cause of LS is still unknown, autoimmune association and genetic susceptibility are suggested. In one study it was found that the presence of human leukocyte antigen (HLA)-DQ7 is associated with early onset of LS, and the family history of autoimmunity is strongly associated in this group. While conventional treatment usually consists of topical corticosteroids, recent reports suggest that topical tacrolimus is effective for vulvar LS. According to our researches the first case report of low-concentration of tacrolimus was made by *Matsumoto* et al [2]. We describe here a case of childhood vulvar LS in which we used tacrolimus treatment and it showed a very good effect.

Case Report

A 6-year-old girl visited our department complaining of genital itching with a duration of 1 year and having painful defecation for nearly 2 years. She had also burning pain and dysuria. Physical examination showed white sclerotic

Figure 1. Vulvar and perianal lichen sclerosus (LS) showing whitish sclerotic plaques

skin changes surrounded by a erythematous border in the vulvar and perianal region (**Figure 1**). A biopsy specimen obtained from the labia major showed typical histological features of LS, epidermal ortohyperkeratosis, hipergranulosis, colloid body present in the basal layer. In the subepidermal papillar dermis a band-like lymphocytic and histiocytic infiltration was present (**Figure 2**).

The patient had used local steroids before but there was no any improvement. We applied 0.03% topical tacrolimus (Protopic, *Astellas Pharmaceutical*) ointment once a day. Clinical examination and recording of patient symptoms was performed before, after three weeks and after three months of therapy. After three weeks there was an improvement of pruritus, dysuria and painful defecation. The erythema around the lesion was decreased. After six weeks the erythema was completely disappeared and the skin lesions resolved completely after 10 weeks (**Figure 3**).

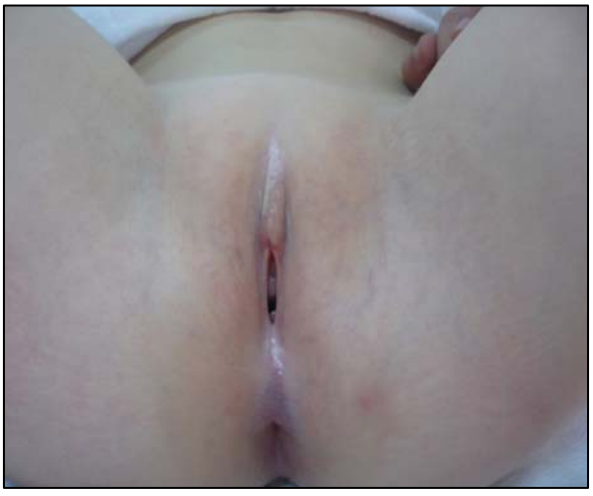

Figure 3. After 6 weeks of treatment with 0.03% tacrolimus ointment.

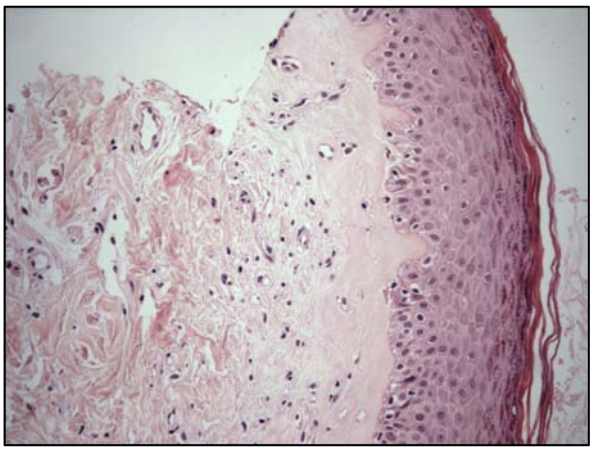

Figure 2. Biopsy showed typical histological features of LS, epidermal ortohyperkeratosis, hipergranulosis, colloid body present in the basal layer. In the subepidermal papillar dermis a band-like lymphocytic and histiocytic infiltration was present (HE)

Discussion

Topical corticosteroids remain the primary treatment of vulvar LS, with evidence for efficacy indicated from several small case studies. Super potent corticosteroids, such as betamethasone clobetasol and clobetasol propionate, have provided satisfactory results in vulvar LS including childhood vulvar LS. However, LS requires continuous topical steroid treatment because of a high recurrence rate of up to 82% after stopping steroids. In addition, long-term use of super potent topical corticosteroids can cause skin atrophy and teleangiectasia [2]. The first report of the use of topical tacrolimus which does not induce skin atrophy in the treatment of vulvar lichen sclerosus was made by *Assmann* et al. The immunomodulatory macrolide tacrolimus acts by inhibition of calcineurin, leading to an inhibition of nuclear gene transcription of interleukin 2 and several other pro-inflammatory cytokines. Consequently, activation and differentiation of T cells and other inflammatory cells are suppressed. Tacrolimus ointment reveals therapeutic efficacy and safety in short- and long-term treatment of atopic eczema in adults and children. Regarding that T lymphocytes and other inflammatory cells are direct targets of tacrolimus [3]. Complete remission was obtained in our case within 12 weeks by application of 0.03% topical tacrolimus once daily. *Böhm* et al. reported that the tacrolimus blood levels in the patients treated with 0.03% topical tacrolimus were below or at the detection limit;

They believe that the defective barrier in the inflamed anogenital skin and the natural occlusion in this intertriginous area largely contribute to the efficacy of topical tacrolimus. Since penetration may be higher in early or erosive lesions than in fibrosclerotic skin, treatment of lichen sclerosus with tacrolimus should be initiated as soon as possible [4]. That is why in this case we choosed to use topical tacrolimus as the first choice of treatment. Prognosis of childhood LS remains unknown. Although childhood LS was once suggested to resolve at puberty, several studies have shown that the disease usually persists after puberty despite symptomatic improvement [5, 6]. The disease in women may be associated with development of vulvar SCC. Ideally, long-term follow-up should be the standard of care [5].

The lifetime risk of squamous cell carcinoma (SCC) with known vulvar LS is estimated to be 4–5% [2]. *Vilmer* et al [7] suggested the protective effect of a potent steroid treatment from malignant evolution, as in their series SCC developed only in untreated or uncontrolled vulvar LS [7]. According to this finding the early treatment and careful follow up will be helpful in the protection against SCC.

The efficacy of calcineurin inhibitors in LS is mainly due to their antipruritic effect currently is believed to be related to the inhibition of inflammatory cytokines. Furthermore, recent investigations indicate a release of neuropeptides from sensory nerve fibers and degranulation of mast cells mediated by pimecrolimus and tacrolimus [8]. According to *Boms* et al they observed that subjective symptoms such as pruritus and pain completely resolved after a few weeks of treatment and clinical features such as fissuring, purpura, inflammatory erythema and genital bleeding almost completely resolved at the end of therapy of topical pimecrolimus. The white sclerotic lesions could however not be changed significantly [9]. We received the same results by using 0.1% topical tacrolimus.

According to *Hengge* et al [10] topical tacrolimus 0.1% ointment also seems to be an effective and safe off-label therapy for the long-term treatment of lichen sclerosus.

As a conclusion, tacrolimus ointment appears to be a promising option for vulvar LS as there is a symptomatic relief at puberty in pediatric patients, To confirm the safety and efficacy of this novel drug, further controlled clinical trials and careful long-term follow up is necessary.

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