Successful Treatment of Vulvar Lichen Sclerosus With Topical Tacrolimus

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 19-year-old woman was admitted to our department with a history of itching and pain of the vulvar region. During a period of 6 months, her clinical symptoms had significantly deteriorated resulting in painful urination and defecation in addition to dyspareunia. Clinical examination showed well-demarcated, smooth, whitish shiny plaques that affected the labia minora, introitus vaginae, and the clitoral hood. Lesions extended to the posterior fourchette, perineum, and anus. The mucosa appeared thin and fragile with a cellophane paper–like texture. The clinical picture suggested a diagnosis of lichen sclerosus.

To rule out differential diagnoses including lichen planus, cicatrical pemphigoid, morphea, and intraepithelial neoplasia, a skin biopsy specimen was obtained. Histopathologic examination displayed pronounced hydropic degeneration of the basal cell layer, edema, homogenization of collagen in the upper dermis, and a prominent bandlike inflammatory infiltrate in the lower dermis. These findings confirmed the diagnosis of lichen sclerosus (also known as lichen sclerosus et atrophicus). Gram stains of cervical, vaginal, and urethral swabs revealed regular epithelial cells and lactobacilli without signs of inflammation. Human papillomavirus (HPV) DNA was not detected by hybridization tests of vulvar and perianal swabs. Autoantibodies to a variety of targets (nuclear, microsomal, and thyroid) were not detected.

Application of diflucortolon-21-valerate twice daily for 2 months only moderately improved the clinical presentation and the physical complaints. The beneficial effect was short-lived; tapering of the corticosteroid use resulted in a prompt relapse. Once-daily treatment with 250-mg doses of oral chloroquine for 4 months in combination with topical estrogen and/or topical 0.025% tretinoin failed in our patient.

THERAPEUTIC CHALLENGE

Numberous treatment options for lichen sclerosus have been proposed, but therapeutic results are often of limited efficacy and provide only temporal relief. Potent corticosteroids applied topically are generally considered the first-line treatment.1-3 None of the therapeutic regimens used in our patient, however, were sufficiently beneficial. The patient continued to refrain from sexual intercourse owing to severe vulvar discomfort. Urination and defecation remained painful and frequently required analgesic medication. The challenge was to find a safe and effective alternative therapy to induce long-term improvement or complete remission of the disease.

SOLUTION

Therapy was initiated with compounded 0.1% tacrolimus (FK506) ointment applied twice daily to affected areas. The macrolide compound was incorporated into a formulation of white petrolatum, mineral oil, propylene carbonate, white wax, and paraffin by the institutional pharmacy department. During follow-up visits after 2, 4, 6, 9, and 12 weeks, the patient reported progressive improvement of the clinical symptoms. Pain and burning sensations had disappeared after 6 weeks, and the patient was able to resume sexual intercourse by 12 weeks of 0.1% tacrolimus application. Complete resolution of visible lesions was observed another 4 weeks later, and therapy with topical tacrolimus was stopped after 6 months of continuous application twice daily. Except for mild temporary burning sensations shortly after application of the ointment, no adverse effects were reported. Blood pressure, blood cell counts, and blood chemistry values remained unchanged, and no systemic adverse effects attributable to tacrolimus ointment were detected. Twelve months after cessation of therapy, the patient continued to be asymptomatic without clinical recurrence of lichen sclerosus lesions.

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Lichen sclerosus is a chronic inflammatory disease of unknown cause. Any anatomic skin site may be involved, but lichen sclerosus most commonly affects the anogenital region (85%-98% of cases). In a series of 339 patients, the male-female subject ratio was 1:10. Lichen sclerosus can affect all age groups with a higher incidence of onset during early childhood and after menopause. Typically, the eruption begins as an area of pallor, with white, waxy, polygonal papules that coalesce into shiny plaques. The skin is thinned and atrophic and shows disruption of its regular architecture. Frequently, erosions and tender fissures in the labial sulci and perianal area occur. In long-standing disease, many patients experience progressive scarring of the vulva leading to obliteration and fusion of the labia and the perianal structures. The most common symptoms are pruritus, soreness, burning pain, dyspareunia, dysuria, or even constipation. Lichen sclerosus may result in significant psychosocial distress and anxiety severely affecting quality of life.

A likely but unproven cause of lichen sclerosus involves an autoimmune mechanism. Although various autoantibodies directed against thyroid, microsomal, nuclear, and mitochondrial antigens have been reported to be more common in patients with lichen sclerosus than in healthy controls, these autoantibodies were not detected in the patient described herein. The end stage of lichen sclerosus is irreversible scarring that causes substantial morbidity, thus emphasizing the need for a safe and long-lasting therapeutic option.

Lichen sclerosus was historically treated with keratolytic, caustic, or irritating agents including salicylic acid, trichloroacetic acid, and thymol. Until the 1950s, various forms of radiotherapy were used for the treatment of lichen sclerosus, followed by the systemic application of bismuth. Surgical approaches including vulvectomy, cryosurgery, and carbon dioxide laser vaporization have also been advocated as treatment options. In a series of 339 patients, the male-female subject ratio was 1:10. Lichen sclerosus can affect all age groups with a higher incidence of onset during early childhood and after menopause. Typically, the eruption begins as an area of pallor, with white, waxy, polygonal papules that coalesce into shiny plaques. The skin is thinned and atrophic and shows disruption of its regular architecture. Frequently, erosions and tender fissures in the labial sulci and perianal area occur. In long-standing disease, many patients experience progressive scarring of the vulva leading to obliteration and fusion of the labia and the perianal structures. The most common symptoms are pruritus, soreness, burning pain, dyspareunia, dysuria, or even constipation. Lichen sclerosus may result in significant psychosocial distress and anxiety severely affecting quality of life.

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Histopathologically, lichen sclerosus resembles other immunologically mediated skin diseases such as graft-vs-host disease, which suggests that activated lymphocytes may play a role in the pathogenesis of lichen sclerosus. This provides a rationale for the use of tacrolimus. This substance is a potent macrolide immuno-suppressant that has been widely used systemically to prevent allograft rejection in liver, kidney, and heart transplantation since the late 1980s. Its mechanism of action has been studied in detail. Tacrolimus binds to cytosolic proteins inactivates the calcium-dependent phosphatase calcineurin that results in a suppression of nuclear factor κB-dependent cytokine gene transcription in T cells. Recent experimental data indicate that topical tacrolimus interferes with the epidermal cytokine network and inhibits epidermal cytokine messenger RNA expression, including tumor necrosis factor α, interleukin (IL) 1α, IL-1β, sargramostim, and macrophage inflammatory protein 2. This effect is accompanied by impaired induction of a T helper 1 (IL-2 and interferon γ) and T helper 2 (IL-4) cytokine response resulting in suppression of T-cell activation and T-cell migration in vivo.

The clinical efficacy of both topical and systemic application of tacrolimus has been reported in several inflammatory skin diseases, including psoriasis, Behçet disease, and pyoderma gangrenosum. Recently, a multicenter study demonstrated that topical tacrolimus is also effective in atopic dermatitis. In this study, blood concentrations of tacrolimus were determined after topical application of this drug. When 0.1% tacrolimus ointment was applied to defined areas ranging from 200 to 1000 cm², the highest blood concentration measured was 2.4 ng/mL, while a large group of patients had values below the detection limit. In comparison, the therapeutic range for tacrolimus in organ transplant patients is between 15 and 20 ng/mL.

Recently, Vente et al treated 6 patients who had severe mucosal lichen planus with topically applied 0.1% tacrolimus ointment. After 4 weeks, complete resolution was observed in 3 patients and substantial improvement in the remaining 3. Blood levels of tacrolimus after topical application to the oral mucosa were below the detection limit in 5 of 6 patients. Thus, since our patient applied 0.1% tacrolimus ointment to an area smaller than 60 cm², the risk for systemic adverse effects is exceedingly low. When vulvar lichen sclerosus is treated with topical corticosteroids, most patients require long-term regular application. In contrast, our patient has no clinical signs of relapse 12 months after the cessation of tacrolimus therapy. Moreover, topical tacrolimus does not seem to have the atrophogenic effect of corticosteroids because it does not interfere with collagen synthesis.

In conclusion, the introduction of topical tacrolimus for the treatment of chronic T cell–mediated inflammatory skin diseases has shown significant efficacy and an excellent safety profile with few notable local adverse effects and a minimal risk of systemic adverse effects. The present case indicates for the first time that topical tacrolimus could serve as a potent, long-lasting, and safe addition to the armamentarium for the treatment of lichen sclerosus.

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REFERENCES


