Acitretin therapy for vulvar lichen sclerosus complicated by recurrent squamous cell carcinoma

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INTRODUCTION

Lichen sclerosus (LS) is a chronic, idiopathic inflammatory disorder with a predilection for the vulva, perineum, and perianal skin. It is characterized by ivory-white scattered to confluent atrophic plaques.[1] Women are affected more often than men, and symptoms include, pruritus, burning, and dyspareunia. Symptoms manifested by vulvar LS (vLS) can have significant side effects on sexual functioning, including tearing of the skin, anxiety surrounding sexual activity, and anatomic changes.[2]

The most serious complication of vLS is the development of vulvar squamous cell carcinoma (vSCC). If untreated, the lifetime incidence of vSCC is estimated at 3.5%-7%.[3] Precursor lesions to vSCC include vulvar acanthosis with altered differentiation (VAAD) and vulvar intraepithelial neoplasia. VAAD is an uncommon proliferation of the vulvar squamous epithelium that may have the potential to progress to invasive carcinoma, which may itself be a variant of hypertrophic LS.[4,5] Vulvar intraepithelial neoplasia is a high-grade intraepithelial squamous lesion; the human papillomavirus-unrelated differentiated vulvar intraepithelial neoplasm (dVIN) is associated with vLS and more likely to progress to vSCC than the human papillomavirus-related usual type, now more often referred to as high-grade squamous intraepithelial lesion.[6] When it progresses, dVIN is usually associated with well-differentiated vSCC. Surgical intervention is typically required for the management of vulvar intraepithelial neoplasia and vSCC but remains controversial for VAAD.

Here, we report a case of longstanding vLS complicated by VAAD, dVIN, and recurrent vSCC, which has been successfully managed with acitretin in combination with topical agents.

Abbreviations used:

dVIN:	Differentiated vulvar intraepithelial neoplasm
LS:	Lichen sclerosus
VAAD:	vulvar acanthosis with altered differentiation
vLS:	vulvar lichen sclerosus
vSCC:	vulvar squamous cell carcinoma

CASE REPORT

A 73-year-old woman presented with longstanding pruritus, weeping and irritation of the vulva, perineum, and perianal area since the 1980s. Diagnosis and treatment were delayed until 2002, when she was clinically diagnosed with LS and started on topical clobetasol dipropionate. Her course was complicated by the development of vSCC in 2005. She was initially treated with partial vulvectomy with wide excision of the periclitoral tissue. Histopathology demonstrated a pT2 well-differentiated squamous cell carcinoma with a maximum depth of invasion of 0.5 cm and no lymphovascular invasion. Human papillomavirus immunostaining was not performed.

By 2012, hyperkeratotic plaques developed on the vulva and perianal skin. Over the next 7 years, she had numerous surgical interventions for VAAD, dVIN, and vSCC. During the course of these treatments, the patient managed her vLS with intermittent and inconsistent use of various class I-II topical corticosteroids, including clobetasol dipropionate,

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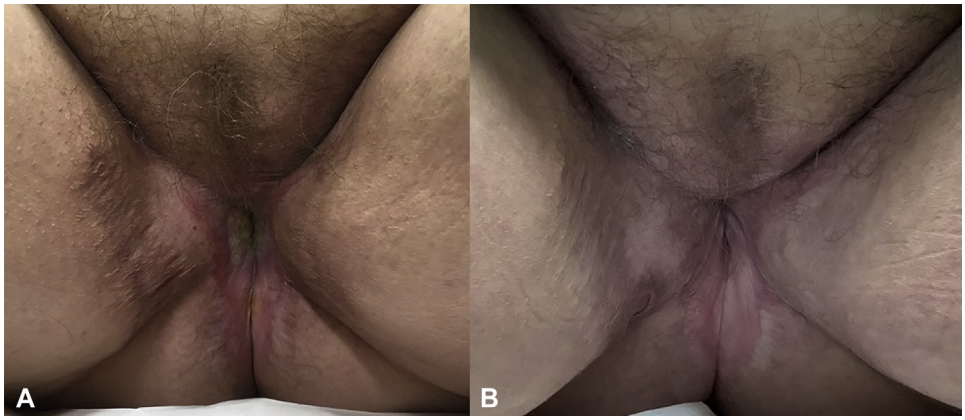

Fig 1. A, Vulva and perianal area on presentation, with extensive postoperative and reconstructive changes to the vulva. Hyperkeratotic white plaques are apparent on the medial aspects of the labia majora at the introitus, surrounded by atrophy and erythema. **B**, After 8 months of acitretin, there was resolution of the hyperkeratotic plaques and improvement of atrophic plaques and erythema. Pruritus and irritation had resolved, and there has been no further scarring of the vestibular orifice.

betamethasone dipropionate, and halobetasol propionate.

A 2013 biopsy demonstrated dVIN with microinvasive foci, and she underwent total vulvectomy. Histopathology demonstrated pT1b well-differentiated squamous cell carcinoma with a maximum depth of 1.1 mm and no lymphovascular invasion, with associated VAAD. Margins were negative for malignancy, but extensive background LS was noted.

In 2016, she had a recurrence of VAAD in a background of hypertrophic LS and underwent CO_2 laser ablation.

In 2017, a left anterior vulvectomy and fulguration were performed due to the presence of a 1-cm raised plaque at the left anterior aspect of the vulva and adjacent hypertrophic tissue. The pathology indicated dVIN with positive margins at the apex, confined to the area of fulguration. Background LS with atypia was noted. Later in 2017, a left posterior vulvectomy showed dVIN in a background of hypertrophic LS, with positive margins. Periurethral and 3 perianal biopsies demonstrated LS without malignancy.

In 2018, a total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and radical vulvectomy with internal reconstruction, including laparoscopic ileostomy, distal urethrectomy, cystostomy with suprapubic catheter placement, and distal vaginectomy, was performed. These procedures were performed due to postmenopausal bleeding, with reconstruction due to extensive scarring. Histopathology demonstrated extensive atypical squamous mucosa with foci of hypertrophic LS, VAAD, and dVIN but without evidence of vSCC. The surgical margins were negative for atypia but positive for LS.

Following the 2018 surgery, hyperkeratotic and atrophic friable plaques developed on the patient's labia, perineum, and perianal areas while using class I topical corticosteroids regularly. Multiple biopsies during 2019 demonstrated hypertrophic LS with occasional atypia but without dysplasia or malignancy.

On presentation to our connective tissue disease clinic in late 2019, the patient noted persistent severe pruritus and irritation of the vulva despite twice-daily application of both halobetasol propionate ointment 0.05% and tacrolimus ointment 0.1%, as prescribed by her referring provider. Examination revealed extensive postoperative and reconstructive changes to the vulva, with obliteration of the labia minora and clitoris, near-complete loss of the labia majora, and narrowing of the vaginal introitus to <2 cm. Thickened, hyperkeratotic white plaques were noted along the medial aspects of the labia majora at the introitus, surrounded by background atrophic erythema and ivory-white dyspigmentation (Fig 1, *A*).

The patient was started on 25 mg of acitretin daily, and her topical regimen was narrowed to halobetasol propionate ointment 0.05%. Within 2 months, the patient noted subjective improvement in pruritus. Five months after the initiation of acitretin, she noted alleviation of pruritus and irritation, resolution of hyperkeratotic plaques, and marked improvement of atrophic plaques and erythema (Fig 1, *B*). Due to arthralgias and diffuse nonscarring alopecia attributed to acitretin, her dose was decreased to 10 mg daily, and she has remained well-controlled to date.

DISCUSSION

The first-line treatment for vLS are class I topical corticosteroids.[7] It has also been noted that inconsistent use of topical corticosteroids may predispose patients to vSCC.[7] While concerns may exist over the use of topical corticosteroids and skin atrophy after prolonged use, the modified mucous membranes primarily affected in vLS are relatively resistant to atrophy. Topical calcineurin inhibitors, such as tacrolimus ointment, may be beneficial but may be less effective than topical corticosteroids and are frequently associated with the sensation of burning upon application, particularly in the genital area.[8]

Acitretin was efficient in a randomized, controlled trial in reducing both signs and symptoms of moderate-to-severe vLS, though its use may be limited by mucocutaneous side effects.[1] Acitretin is a vitamin-A derivative, which activates the nuclear retinoic acid receptor, resulting in inhibition of cell proliferation and tissue infiltration by inflammatory cells, which is postulated to help mitigate the inflammation seen in vLS.[9] Low-dose acitretin has also been demonstrated to reduce the development of cutaneous squamous cell carcinoma in organ transplant recipients, and there is evidence to indicate that it may decrease the development of nonmelanoma skin cancers in nontransplant patients, including those with basal cell nevus syndrome, xeroderma pigmentosum, and cutaneous T-cell lymphoma.[10]

Acitretin therapy was selected for this patient because of its demonstrated efficacy for moderate-to-severe vLS and lack of associated immunosuppressive effects in the setting of recurrent vSCC. Although acitretin has not been previously shown to prevent the development of vSCC, we are hopeful that it is demonstrated chemopreventive effect on cutaneous squamous cell carcinoma may extend some protection against vSCC in this patient.

Conflicts of interest

None disclosed.

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