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Use of topical imiquimod in the treatment of VIN: a case report and review of the literature

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ABSTRACT

Vulvar intraepithelial neoplasia (VIN) is a premalignant disease of the vulvar squamous epithelium. Standard treatment for VIN lesions is surgical excision. Alternative therapeutic options for conservative treatment have been sought by patients to prevent disfigurement and to preserve sexual function. We present such a patient in whom topical imiquimod was used with a successful outcome. Imiquimod is effective in the treatment of VIN, as well as convenient, self-administered, and generally well tolerated.

Introduction

Vulvar intraepithelial neoplasia (VIN) is a premalignant disease of the squamous epithelium. It is described as a proliferation of abnormal keratinocytes limited to the epidermis without invasion of the basement membrane. Historically, various terms have been used to define cancer precursors of the vulva including VIN grades 1-3 and Bowen's disease. In 2004, the International Society for the Study of Vulvovaginal Disease reclassified VIN to refer only to high-grade intraepithelial lesions of the vulva, including older clinical terms such as *Bowen's disease*, *dysplasia*, and *squamous cell carcinoma in situ* (Scurry and Wilkinson, 2006).

VIN is classified into two distinct subtypes. Usual type is associated with high-risk oncogenic human papillomavirus (HPV) infection, cigarette smoking, and immunodeficiency. The less common differentiated type typically occurs in postmenopausal women and is associated with chronic dermatoses, including lichen sclerosis, and HPV-negative vulvar cancer. Although VIN is an uncommon disease, incidence is increasing, particularly in women younger than the age of 50 years. The clinical presentation of VIN is diverse, and patients may be asymptomatic or have severe pruritus, pain, burning, and dyspareunia.

Treatment of VIN is indicated to decrease progression to invasive disease along with relieving symptoms. Due to the rare incidence of VIN, there are few large randomized studies, and consequently limited data from which to form guidelines for treatment and follow-up. Surgery, with wide local excision or vulvectomy, is currently the standard of care for the treatment of VIN. It allows examination of tissue margins, which is especially helpful in invasive disease. However, surgery often results in significant morbidity, including sexual and psychosocial dysfunction, and is associated with a high rate of recurrence (Lai and Mercurio, 2010). Alternatively, medical management of VIN has been investigated. Nonsurgical therapy may prevent disfigurement and preserve sexual function, but is limited to patients with no evidence or suspicion of invasive disease on clinical exam or biopsy. Available therapeutic options for conservative treatment of VIN include imiquimod, cidofovir, indole-3-carbinol, photodynamic therapy, and laser ablation (Hillemanns et al., 2006; Lai and Mercurio, 2010).

Imiquimod is an immune response-modifying agent currently FDA approved for the topical treatment of actinic keratosis, superficial basal cell carcinoma, and external genital warts. Although a number of studies support the use of topical imiquimod for the conservative treatment of VIN, clear guidelines for optimal treatment duration and follow-up timeline have not yet been determined. We report a case of a woman who was diagnosed with unifocal VIN and treated with 5% topical imiquimod cream with complete response.

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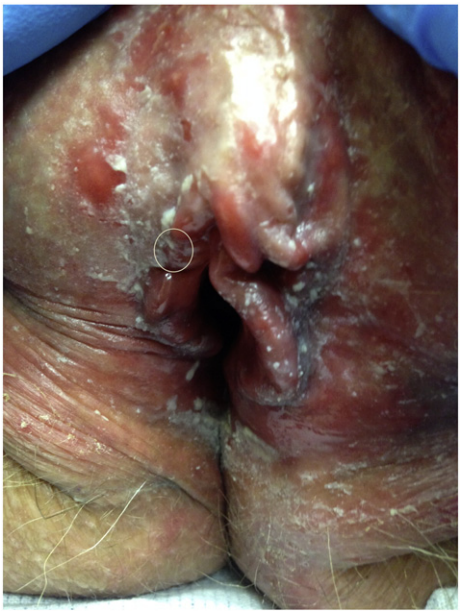

Fig. 1. 5×3 mm white plaque on the right aspect of the clitoral hood during imiquimod therapy.

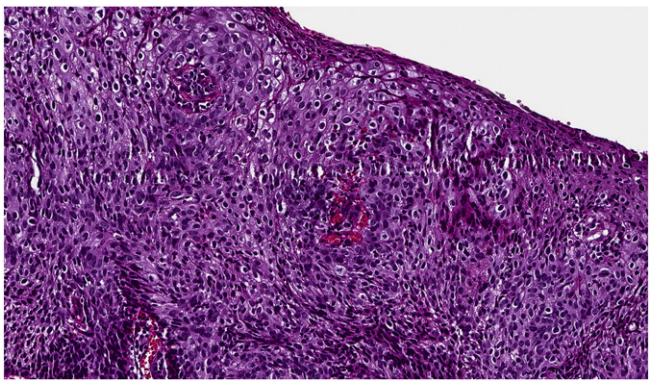

Fig. 2. Pretreatment histopathology: Full-thickness involvement of the vulvar mucosa by a proliferation of markedly atypical, hyperchromatic cells with high nuclear-to-cytoplasmic ratio, and irregular nuclear borders. Some cells show cleared out cytoplasm, suggesting human papillomavirus (HPV) effect (H&E, 20×).

Case Report

A 75-year-old woman was referred to our dermatology department for an asymptomatic vulvar lesion of unknown duration. The lesion was histologically classified as HPV-related VIN with full thickness atypia. The patient was interested in pursuing nonsurgical options before resorting to vulvectomy. She denied pruritus, pain, dysuria, and dyspareunia. No prior treatments had been tried.

Physical exam revealed a 5×3 mm white plaque on the right aspect of the clitoral hood (Fig. 1). Initial biopsy of the lesion demonstrated full-thickness marked atypia, occasional cleared out cytoplasm (haloes), and parakeratosis, most consistent with HPV-related VIN (Fig. 2).

Treatment was initiated with topical imiquimod 5% cream, five times per week, for 12 weeks. The lesion was re-evaluated after 12 weeks of treatment and repeat biopsy was performed. Subsequent biopsy showed moderate to severe squamous dysplasia confined to the basal cell layer with an intense lichenoid inflammatory reaction (Fig. 3). No VIN was seen. We repeated an additional course of topical imiquimod 5% cream, five times per week for an additional 12 weeks. Shave biopsy after 24 weeks of imiquimod therapy demonstrated lichenoid dermatitis with no residual dysplasia or carcinoma (Fig. 4). Side effects included local irritation, pain, and candidal infection during the course of treatment. Treatment was stopped and patient was evaluated at 3, 6, and 9 months without signs and symptoms of recurrence (Fig. 5).

Discussion

Imiquimod, a heterolytic imidazoquinoline amide, is an effective alternative to surgery for the treatment of VIN. Classified as an immune response-modifying drug, imiquimod enhances local skin immune responses by activating toll-like receptor-7 and -8 on macrophages and dendritic cells, which induces the release of pro-inflammatory T-helper cell type 1 cytokines (interferon-α, interleukin-2, interleukin-12) and upregulates cell-mediated immunity (Sauder, 2000). This results in an antiviral and proapoptotic effect on HPV-infected abnormal cells. Side effects include local pruritus, pain, burning, irritation, and soreness, which are generally well tolerated. Patients with biopsy-proven invasive disease are excluded from medical management. Surgical treatment should be considered for lesions that do not respond to medical therapy.

A number of studies support the use of topical imiquimod as the conservative treatment of choice for women with VIN (Table 1). In a review of three clinical trials, the frequency of application of imiquimod 5% cream ranged from two to three times weekly, with some studies employing slow frequency escalation (Le et al., 2007; Mathiesen et al., 2007; van Seters et al., 2008). The duration of treatment lasted 16 weeks in all studies, and follow up ranged from 2 months to more than 7 years. The results of these studies demonstrated complete response rates ranging from 30 to 81%, partial response from 9.5 to 38%, and no response from 9 to 30%.

Based on a review of the literature, small (<1 cm) lesions are more likely to demonstrate a complete response to imiquimod treatment. However, treatment periods in the randomized controlled trials may have been too short to be effective for larger (>5 cm) lesions. A significant association was seen between the local skin reaction achieved and complete disease regression. Those that reached a higher degree of local irritation had a better likelihood of observed complete response to treatment (Le et al., 2007). Another potential predictive marker of imiquimod response includes viral clearance, as complete histologic regression of lesions strongly correlates with HPV clearance ($p < .001$) (van Seters et al., 2008). Patients with

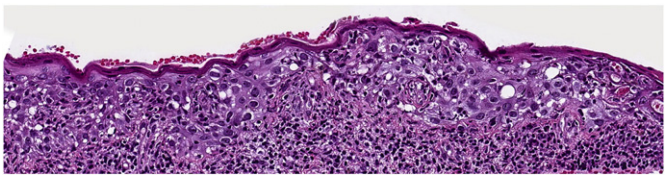

Fig. 3. Twelve-week histopathology: Subtotal involvement of the vulvar mucosa by moderate to severe squamous dysplasia. Intense lichenoid inflammatory infiltrate noted in the underlying submucosa (H&E, 20×).