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Treatment of Multifocal Bowen's Disease in Immunocompromised Women With Surgery and Topical Imiquimod

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Abstract

Background—In human immunodeficiency virus (HIV)-infected women, Bowen's disease may be difficult to successfully treat with surgery alone. Imiquimod cream, effective in treating Bowen's disease in healthy women, may be a useful postsurgical treatment in immunocompromised women.

Case(s)—Two HIV-infected women had both Bowen's disease and severe cervical dysplasia. In both cases, Bowen's disease, but not cervical dysplasia, recurred after surgical treatment. When treated with topical 5% Imiquimod cream twice weekly for 4 months, 70-80% reduction in lesions were observed in both patients. Follow-up biopsies of remaining lesions were vulvar intraepithelial neoplasia (VIN) 1.

Conclusion—Imiquimod cream, in combination with surgical treatment, may be an appropriate strategy for treatment of Bowen's disease in HIV-infected and other immunocompromised women.

Introduction

Persistent human papillomavirus (HPV) infection in human immunodeficiency virus (HIV)-infected women is associated with genital tract neoplasia such that cervical cancer is considered an acquired immunodeficiency syndrome (AIDS) defining disease (1). In HIV-infected women, similar to cervical dysplasia, extensive, multifocal Bowen's disease can occur, surgical therapy with local excision or laser removal may be only temporarily effective, and relapse is common (2).

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Imiquimod, an imidazoquinoline amine topical agent, acts through toll-like receptors (TLR) 7 and 8 inducing interferon alpha, IL-6 and tumor necrosis factor alpha. These factors activate antigen-presenting cells resulting in a profound T-helper cell-mediated antitumor cellular immune response (3). Imiquimod has been approved for topical treatment of genital and perianal warts with demonstrated efficacy in treatment of Bowen's disease and vulvar intraepithelial neoplasia (VIN) in healthy women (4-6), but there have been mixed results as the sole treatment of anogenital warts in HIV-infected men and women (7, 8) HIV-infected women and men on highly active antiretroviral therapy (HAART) have a higher response rate with imiquimod treatment of anogenital warts as compared to HIV-infected patients not treated by HAART, with complete responses induced in 31% of patients on HAART and only 11% of patients not on HAART(7, 9).

We report successful treatment of multifocal Bowen's disease with prolonged use of imiquimod after surgical excision in two HIV-infected women on antiretroviral therapy (ART) which in our institution comprises only HAART.

Cases

Two HIV-infected women on antiretroviral therapy (ART) aged 29 and 41, had extensive, biopsy-proven Bowen's disease and severe cervical dysplasia. Informed consent was obtained prior to treatment. All procedures were conducted as part of an institutional review board approved protocol.

The first patient underwent surgical excision and laser ablation of many labial VIN 1/2 lesions and loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia CIN 2/3. She had a recurrence of CIN 2 and multifocal Bowen's disease 18 months later and underwent cone biopsy and a second laser ablation of vulvar lesions. She then received imiquimod treatment for vulvar lesions recurring soon after surgery; cervical disease did not recur. Her CD4 T cell count ranged between 676-734/mm³ throughout imiquimod treatment.

The second patient had just completed treatment for primary CNS lymphoma with 6 cycles of high dose methotrexate and rituximab followed by 2 cycles of consolidation methotrexate. She had been receiving ART for less than 6 months at the time of laser ablation for Bowen's disease and cone biopsy for CIN 3 a month after completing lymphoma chemotherapy. Within two months of surgical intervention, she had recurrence of multifocal Bowen's disease which worsened over the next couple of months (Figure 1A and 1B); cervical dysplasia did not recur. Her CD4 T cell count ranged between 212-318/mm³.

Both patients were treated with twice weekly topical application of 5% imiquimod cream for 4 months, tolerating treatment well without local irritation. A 70-80% reduction in lesions was observed after at least 4 months of treatment; repeat biopsies were VIN 1. Imiquimod, continued in the second patient for 40 weeks, resulting in nearly complete resolution of Bowen's without significant side effects (Figure 2A and 2B).

Comment

In immunocompromised women with HIV, persistent HPV infection predisposes not only the cervical, but also the vulvar squamous epithelium to dysplasia and cancer. In evaluating HIV-infected women for HPV disease, vulvar symptoms, especially chronic pruritus, should trigger close inspection of the vulva for lesions. Flat, brown lesions, the hallmark of Bowen's disease, may be extensive and multifocal (10). Untreated Bowen's disease has the potential to become invasive, and thus, must be treated.

Surgical treatment of Bowen's disease includes wide local excision, laser ablation and, in some cases, vulvectomy. In these cases, surgical treatment alone was insufficient to treat Bowen's disease in immunocompromised patients with HIV infection, even though they were on antiretroviral therapy. While some surgeons recommend vulvectomy in cases of recurrent VIN, excisional surgery may not prevent recurrence of Bowen's disease in HIV-infected women (1, 10). Importantly, vulvectomy is disfiguring and may affect sexual functioning in young women. Therefore, a strategy to treat recurrent Bowen's disease, thus preventing progression to invasive cancer while preserving normal anatomy and function is preferable, especially for young women.

Medical treatments for HPV disease include topical agents such as 5-fluorouracil (5-FU) and imiquimod (10). Significant vulvar irritation which may lead to early treatment cessation has been reported with 5-FU. In immunocompetent populations, moderate to severe VIN treated with imiquimod alone had significant response (4) leading to a durable remission (5). In a placebo-controlled, double-blind, randomized clinical trial, 35% of patients experienced a complete response and remained disease-free at twelve months (4). After a median follow up of 7.2 years, VIN recurred in only one of the complete responders (5). In another study, the overall response rate was 77% with a recurrence rate of 20.5% after a median follow-up of 16 months, a significantly lower rate compared to surgically treated cases in their study (53.5%) (6).

Although imiquimod has become a first-line treatment of VIN in immunocompetent populations, lower long-term efficacy rates with use as a sole treatment of VIN in HIV-infected women have been reported. In a randomized case-control study of HIV-infected patients with anogenital warts only, 31% of 75 HIV-positive patients achieved a complete response; 24% experienced a partial response, but no clinical response occurred in 45%. Four of 23 HIV-infected patients experienced recurrence after three months of follow-up (7). Similarly, in a case series of four cases of HIV-positive patients using highly active antiretroviral therapy who were treated with imiquimod alone, a complete response was obtained in one case, and a partial in two (8).

Combining conservative surgical treatment with prolonged treatment with imiquimod initiated in the post-operative period when lesions recur, appears to be an effective, safe strategy in immunocompromised women and warrants further study. The adjuvant use of imiquimod could be preferred over other treatment modalities for Bowen's Disease in immunocompromised women, as it is a self-administered, well-tolerated, non-invasive treatment and does not affect quality of life or sexuality.

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Figure 1.
Recurrence of Bowen's disease in patient 2 indicated by arrows, two months after surgical treatment. A, labia closed; B, labia opened

Figure 2.

After 40 weeks of twice weekly imiquimod treatment, lesions indicated by arrow have nearly resolved and biopsy was consistent with vulvar intraepithelial neoplasia I. LA, labia closed; B, labia opened.