Imiquimod and 5% Fluorouracil Therapy for Anal and Perianal Squamous Cell Carcinoma In Situ in an HIV-1–Positive Man

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REPORT OF A CASE

A 59-year-old human immunodeficiency virus–positive (HIV-1+) white man presented with a nonhealing area that extended extensively around the perianal skin and up into the anal canal. The area had been present for greater than 2 years with an increase in size over the past 6 months. Biopsies were performed, and multiple biopsy specimens sampled from the cutaneous surface as well as within the distal anal canal showed squamous cell carcinoma in situ.

The patient’s HIV-1 disease had been diagnosed approximately 15 years earlier, and had been well controlled during most of that time with antiviral therapy, including protease inhibitors over the past 4 years. The patient’s CD4 cell count was more than 500/µL, and he had an unmeasurable viral load; he had been taking stavudine (40 mg twice daily), lamivudine (150 mg twice daily), indinavir (400 mg twice daily), and nelfinavir (250 mg 3 times per day) for approximately 1 year. Other significant medical history included 5 basal cell carcinomas, both nodular and superficial types, dating from 1990, with the last tumor treated in 1996.

Physical examination revealed an area of perianal erythema with extensive areas of ulceration around the rectum and extending into the rectum (Figure 1). Anoscopic examination showed that the area of visually atypical anal mucosa extended just inside the anal canal.

Multiple biopsies were performed on the involved skin, including the mucosa, to better define the extent of disease.

THERAPEUTIC CHALLENGE

Both radiotherapy and Mohs micrographic surgery for the area of cutaneous involvement followed by surgical excision of the rectum were considered as possible therapies. However, because the patient’s HIV-1 disease was well controlled, he wished to try a less aggressive treatment.

SOLUTION

After we confirmed that the results of viral studies for the herpes simplex virus and bacterial and fungal cultures for pathogens were negative, treatment was started with 5% imiquimod cream on a Monday-Wednesday-Friday schedule. The patient applied the cream at bedtime to the external area of involvement and within the anal canal, washing it off in the morning. The patient also applied daily 5% fluorouracil in the morning to the area of cutaneous involvement and within the anal canal. Although initially the patient experienced some increased irritation, he tolerated the treatment well and continued the therapy for 16 weeks. Clinically and symptomatically, there was gradual improvement after approximately 4 weeks of therapy, and at 16 weeks, there was minimal superficial ulceration with moderate residual erythema. At approximately 12 weeks, the patient showed signs of infection, with increased greenish mucoid material overlying the area of involvement. Cultures showed a mixed bacterial infection. The patient was treated with 2% topical mupirocin ointment, 0.75% metronidazole cream, and oral levofloxacin, 500 mg, for 10 days with clearing of the infection.

The erythema and residual superficial erosions healed rapidly after all therapy was discontinued. Approximately 3 weeks later, a biopsy was again performed on the patient, with specimens taken from multiple sites within the prior area of involvement; 4 of the biopsy specimens came from the area immediately around the rectal opening (Figure 2). In addition, the patient had a Thin-Prep (Cytyc Corp, Boxborough, Mass) cytologic smear performed using both a firm spatula and a brush to sample the anal mucosa extensively, including the areas well proximal to the area of involvement previously defined clinically and histologically. Follow-up clinical examinations, cutaneous biopsy specimens, and mucosal cytologic examination showed no evidence of residual dysplasia.

The initial biopsy specimens showed multiple areas of full-thickness epithelial dysplasia within both the overlying skin and far distal anal squamous mucosa. The cells were markedly atypical and pleomorphic, with large, hyperchromatic nuclei, many with prominent red nucleoli. In addition, there were some epithelial giant cells and numerous mitoses, some atypical, and scattered dyskera-
In situ DNA probes (Pathgene-Enzo Diagnostics, Syosset, NY) for human papilloma virus (HPV) types 6/11, 16, 18, and 31 were performed using standard techniques described by the manufacturer on the initial biopsy sections as well as the sections used to determine the extent of the tumor. Results of the in situ DNA probe for HPV type 16 were positive in the keratinocytic nuclei most numerous in the areas near the periphery of the tumor (Figure 3), but focally positive throughout the tumor. Follow-up cutaneous biopsy specimens showed mild dermal fibrosis with a moderate residual chronic inflammatory infiltrate. Flattening of the rete ridge pattern was seen in all biopsy specimens. The overlying epidermis showed a bland epithelium with ordered differentiation. ThinPrep cytologic examination showed evidence of HPV, but no significant cytologic dysplasia. Follow-up clinical examination, including anoscopy examination, and ThinPrep cytologic examination 3 months later showed no evidence of recurrence of carcinoma in situ.

**COMMENT**

Imiquimod belongs to a family of imidazoquinolines that have potent antiviral and antitumor properties in animal models without any demonstrable direct antiviral or antiproliferative actions. The immune effects of 1- to 5-mg/mL imiquimod appear to be mediated, at least in part, through stimulation of innate immunity. In particular, imiquimod therapy has been associated with release of monocyte-macrophage–derived cytokines, such as interferon alfa (IFN-α), tumor necrosis factor α (TNF-α), interleukin 1α (IL-1α), IL-6, IL-8, IL-12, and prostaglandin E2 (PGE2), resulting in a Th1 dominant response.1-6

Imiquimod has recently been shown to enhance the functional maturation of Langerhans cells, as well as their migration to regional lymph nodes.6,7 Functional maturation and migration of Langerhans cells are necessary for antigen presentation in the development of adaptive immune responses.6,7 In one of these studies, imiquimod was also shown to enhance contact hypersensitivity responses.6 The ability to enhance cutaneous adaptive responses, as well as innate immunologic responses, may be very important in imiquimod’s antiviral and antitumor effects.

The combined effects of Th1 cytokine switching and increased antigen presentation may be particularly helpful in patients with underlying immune deficits, especially those predisposed to a Th2 cytokine switching pattern, ie, those with atopic dermatitis and HIV-1 disease.7,9 Since most effective antiviral and antitumor responses are mediated through the endogenous system the presentation of tumor or viral antigens to CD8+ T cells by major histocompatibility complex class I molecules, this potentiation may still be effective even in patients in whom immune suppression particularly targets CD4+ T cells, such as those with HIV-1 disease.5,9
Because of the extent of disease in our patient, we decided to use combined therapy with both imiquimod and a chemotherapeutic medication, fluorouracil. Fluorouracil has previously been used in the therapy of carcinomas in situ for patients with Bowen disease.\textsuperscript{10-12} Fluorouracil is also the first-line therapy for gastrointestinal carcinomas, and in this context it has been combined with IFN-\(\alpha\), one of the principal cytokines induced by imiquimod, to improve its therapeutic index.\textsuperscript{13-15} Interferons alpha, beta, and gamma all enhance the activity of fluorouracil both in vitro and in vivo.\textsuperscript{16,17}

One mechanism by which they do this is through the induction of the enzyme thymidine phosphorylase, thereby enhancing the conversion of fluorouracil to its active metabolite, 5-fluorodeoxyuridine monophosphate.\textsuperscript{18} This leads to increased depletion of thymidine triphosphate pools and increased DNA fragmentation.\textsuperscript{19,20} Interferon treatments also lead to the abrogation of a fluorouracil-associated increase in the enzyme thymidylate synthase, thus increasing tumor sensitivity to fluorouracil.\textsuperscript{21} Finally, IFN augments plasma fluorouracil levels.\textsuperscript{16,17}

Our patient illustrates a complication for HIV+ patients associated with prolonged survival when these patients are treated with the new, highly effective combined antiretroviral therapies.\textsuperscript{13,14} Infections with multiple oncogenic HPV types are very common among HIV+ homosexual men, and show almost a 100% association with anal squamous cell carcinoma.\textsuperscript{22} Although highly effective combined antiretroviral therapy, with its improvement in the patient’s immune status, has proven effective in dramatically decreasing some viral infections and/or malignancies, eg, molluscum contagiosum and Kaposi sarcoma, HPV infections and their associated malignancies have not responded as favorably.\textsuperscript{18-20}

Both cytology and anoscopy have proven useful in predicting the development of these intraepithelial neoplasms long before they become as extensive as in our patient. Although this patient’s oncogenetic HPV infection may have become latent, it was not cured, and neither was his HIV-1 infection. Thus, treatment with imiquimod alone or in combination with topical chemotherapeutic agents such as fluorouracil or antiviral agents such as cidovir may prove effective in controlling epithelial dysplasia and/or squamous cell carcinoma in this growing patient population but probably will not result in a permanent cure.\textsuperscript{15,18}

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REFERENCES


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