Successful Treatment of Disseminated Human Papillomavirus Infection with Pegylated Interferon and Ribavirin

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We report a case of disseminated human papillomavirus infection that developed in a patient while receiving efalizumab for the treatment of psoriasis. This infection progressed for several months after efalizumab treatment had been stopped. All human papillomavirus lesions completely resolved after 10 weeks of therapy with a combination of pegylated interferon and ribavirin.

Case report. A 26-year-old human immunodeficiency virus (HIV)–negative man presented in October 2008 with progressive disseminated warts in his perianal region, urethra, nasal mucosa, and soles of his feet of 6 months’ duration. He had a history of psoriasis, which had been well controlled with efalizumab (a humanized anti-CD11a monoclonal antibody) treatment since May 2005. In April 2008, he developed perianal warts. A colposcopy at that time revealed multiple warts up to the dentate line, which were fulgurated. By June 2008, the warts had recurred and grown rapidly, precluding flexible sigmoidoscopy. In addition, he developed papillomas in the left nostril and numerous plantar warts that were unresponsive to topical imiquimod. Efalizumab treatment was then stopped.

In September 2008, the patient developed dysuria, and a cystoscopy revealed multiple urethral papillomas in the fossa navicularis. By October 2008, he developed bulky circumferential perianal and anal canal warts up to the anorectal ring. He then underwent surgery to remove warts on the left side of the anal margin. The pathological diagnosis was “condyloma acuminata” and there was no evidence of malignancy. The patient was scheduled for further surgery to remove the remainder of the warts. However, severe pain and discomfort associated with surgical removal, and his previous experience with recurrence after surgical treatment prompted him to pursue other treatment options.

Various options were explored. There are no consistently effective treatment options for disseminated human papillomavirus (HPV) infection [1]. Interferons have been shown to have some efficacy in treatment of genital warts, but local treatments have appeared to have produced better results than systemic treatments in previous studies [2]. However, the disseminated nature of our patient’s disease precluded local treatment. Pegylated interferon has been used for the treatment of HPV-related diseases with some success, but complete remissions have been uncommon [3, 4]. Ribavirin as an adjunct to laser surgery has been reported to be effective for the treatment of juvenile laryngeal papillomatosis [5]. A previous report had noted unexpected resolution of extensive plantar warts in an HIV-infected man while he was receiving a combination of pegylated interferon and ribavirin for treatment of hepatitis C [6]. It was decided to attempt the latter treatment for our patient with the specific intention of treating HPV infection. It was believed that a trial of pegylated interferon and ribavirin was reasonable given the lack of reliably effective treatment options.

In November 2008, the patient began taking pegylated interferon-alfa-2b (120 μg subcutaneously once per week) and oral ribavirin (400 mg orally twice per day). The response to this treatment was dramatic. After just 2 weeks, the patient noticed that some of the warts were decreasing in size. By 6 weeks, all of the lesions were substantially smaller. After 10 weeks of therapy, all of the HPV lesions (perianal, nasal, urethral, and plantar) had completely resolved. The perianal region and sole of his right foot before treatment and after a few weeks of treatment are shown in Figure 1. Follow-up appointments with podiatry, colorectal surgery, and urology clinics were cancelled because they were no longer necessary.

The patient developed the anticipated influenza-like symptoms associated with pegylated interferon. The symptoms were the worst on the day immediately after the injection and gradually improved over the next few days. In addition, he developed a flare of psoriasis on his scalp, hands, feet, and genitals within 1 week after he started pegylated interferon therapy. This was reasonably well controlled with the addition of 15 mg of oral methotrexate per week.

Antiviral therapy was continued for 5 weeks beyond the clinical resolution of all warts due to a concern about relapse of HPV infection. Combination antiviral therapy was stopped in...
February 2009. The patient has not had a recurrence of any warts for >1 year after completion of the antiviral therapy.

**Discussion.** This report describes an association between efalizumab use and the subsequent development of disseminated HPV infection, and successful treatment of the latter with a combination of pegylated interferon and ribavirin. Development of disseminated HPV infection in a patient receiving efalizumab therapy has, to our knowledge, not been described previously. Efalizumab is a humanized monoclonal antibody directed against the CD11a subunit of the leukocyte function-associated antigen 1 [7]. It decreases T cell responses in experimental studies and has been shown to be effective in the treatment of psoriasis [8, 9]. Biological agents have been prominently associated with reactivation of latent infections [10]. Efalizumab is no exception, and infectious complications associated its use have included tuberculosis, disseminated cryptococcal infection, cytomegalovirus colitis, and disseminated eruptive giant mollusca contagiosa. Recently, at least 3 people with psoriasis being treated with efalizumab developed progressive multifocal leukoencephalopathy. This development prompted a voluntary withdrawal of the drug from the market by the manufacturer in 2009.

Histologic examination of a wart often demonstrates lymphocytic exocytosis into the epidermis. T cells that infiltrate HPV lesions develop a proliferative response when exposed to E7 and L1 proteins of HPV, suggesting that T cell responses are an important host response to the presence of HPV infection [11].

Psoriasis is an immune-mediated disease characterized by the occurrence of scaling erythematous papules and plaques. Interferon has been shown to localize more strongly in areas of new and developing psoriatic plaques, compared with chronic plaques [12]. Efalizumab reduces migration of T lymphocytes into the skin [7]. Thus, it is possible that efalizumab reduces the effectiveness of host responses to HPV infection, which may be an explanation for why the patient we describe developed disseminated HPV while receiving treatment.

Our patient was rapidly developing new warts in multiple sites, and there was nothing to suggest that the lesions were going to resolve any time soon. The patient’s response to the combination of pegylated interferon and ribavirin was dramatic and much better than anticipated. The strong temporal association between initiation of therapy and complete resolution of lesions support the assertion that the treatment played a significant part in the patient’s recovery from disseminated HPV infection.

Although this report is intriguing, limitations must be acknowledged. Firstly, it must be emphasized that combination treatment of HPV infections with interferon and ribavirin is off-label use of the medications and should not be considered standard therapy at this time. It is not clear whether the resolution of HPV lesions in our patient was because of direct antiviral effect of the treatment, generalized improvement of cell-mediated immunity, or enhanced local immunity from increased lymphocyte trafficking associated with the interferon-
induced flare of his psoriasis. The progressive worsening of symptoms over months but sudden improvement ≤2 weeks after the patient started treatment strongly suggests, however, that treatment had something to do with improvement. This was not a randomized study, and a placebo effect may be considered, but complete resolution of symptoms from a debilitating state and sustained remission over a year argue against this. Although the combination clearly had a dramatic effect in our patient, the relative contributions of pegylated interferon and ribavirin to the therapeutic success are not clear. Plantar warts are usually caused by different genotypes than those that cause genital lesions. Genotyping of our patient’s HPV was not done, and so we do not know whether all of his lesions were caused by a single genotype or multiple genotypes of HPV; thus, it is not clear whether this treatment will be as effective in the treatment of all genotypes. Despite these limitations, this report describes dramatic results in treating a patient with disseminated HPV infections and warrants further investigation into the effectiveness of the treatment prescribed.

This report adds to the list of serious infections occurring in association with treatment with biological agents. It also raises optimism for a potential therapy that may be beneficial for at least some patients with debilitating HPV infections.

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References