Progressive Orf Virus Infection in a Patient with Lymphoma: Successful Treatment Using Imiquimod

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Orf virus is a parapoxvirus that infects small ruminants worldwide. We present the case report of a 73-year-old woman with non-Hodgkins lymphoma who developed progressive orf virus lesions that were unresponsive to surgical debridement and to cidofovir therapy. The patient’s orf virus infection was successfully treated with topical imiquimod despite progression of her malignancy.

Orf virus is a parapoxvirus that infects small ruminants and causes “echyma contagiosum” (also known as “scabby mouth,” “sore mouth,” or “contagious pustular dermatitis”), a vesiculoulcerative disease of both keratinized skin and mucosal surfaces. Orf virus is found worldwide, including in the United States [1]. Humans with healthy immune systems who have contact with infected animals or fomites [2] develop self-resolving cutaneous ulcers, usually on the distal upper extremities. A person with significant T cell dysfunction may develop atypical lesions (i.e., “giant” orf) and/or have a protracted course of illness [3]. Because the disease is usually self-limited, infected humans do not often seek medical attention, especially if they are familiar with the disorder (e.g., if they reside in a farming community) [4]. As a result, the true disease burden among humans is unknown, and therapeutic options have not been well characterized. We present a case of orf virus infection in a woman with progressive lymphoma who was successfully treated with imiquimod after her lesions continued to worsen despite debridement and application of topical and intraleisonal cidofovir.

Case report. A 73-year-old white woman with a history of unremitting follicular, predominantly small-cleaved cell non-Hodgkin lymphoma and rheumatoid arthritis who lived and worked on a farm housing sheep, goats, poultry, and farm cats presented to her primary care physician on 16 May 2005 with several painful, friable vascular noduloulcerative skin lesions that had developed over a 3-week period on both upper extremities (figure 1). The patient recalled bottle-feeding kid goats that were noted to have perioral crusting. On the day of her visit, she was referred to a dermatologist who performed a shave biopsy of lesions on her right forearm and left hand; the differential diagnosis included orf virus infection, bacillary angiomatosis, and cutaneous lymphoma. Pending the biopsy results, therapy with doxycycline (100 mg twice daily) was initiated in consideration of bacillary angiomatosis.

The histopathologic examination revealed vascular proliferation, spongiform degeneration, and viral cytopathic changes in keratinocytes characterized by ballooning degeneration, eosinophilic cytoplasmic inclusions, and irregularly shaped nuclei, consistent with a parapoxvirus infection (figure 2A). Histopathologic evidence of bacillary angiomatosis or cutaneous lymphoma was not observed. The formalin-fixed, paraffin-em-
bedded skin biopsy specimen was evaluated at the Centers for Disease Control and Prevention (Atlanta, GA) using an immunohistochemical staining technique with a polyclonal bovine antipseudocowpox virus (another member of the parapoxvirus genus) antibody. Viral antigens were detected in scattered foci of the lesion in the cytoplasm of keratinocytes showing viral cytopathic changes (figure 2B). PCR performed at the Centers for Disease Control and Prevention on vesicular fluid yielded positive results, using both parapoxvirus generic and orf species–specific real-time primer pairs.

On 26 May, the patient returned to her primary care physician, because she was experiencing increasing pain; doxycycline therapy was discontinued, and cefalexin therapy was initiated at 500 mg 4 times daily for presumed superinfection of the patient’s orf lesions. On 7 June, the patient was referred to a plastic surgeon and underwent an excision and debulking of her orf lesions because of their clinical progression. On 8 June, she developed fever, rigors, nausea, vomiting, and worsening erythema and pain at the excisional site; she was admitted to the hospital for intravenous vancomycin therapy, and blood and wound cultures obtained at that time were all negative for bacterial and fungal pathogens. On 9 June, the patient underwent a bone marrow biopsy to assess her response to fludaraabine and rituximab. The results of tests performed on her bone marrow aspirate revealed that 50% of the marrow space was involved with follicular lymphoma. The specimen was negative for viral cytopathologic changes. The patient was discharged from the hospital on 11 June with a prescription for topical 3% cidofovir (weight-to-volume in an aquaphor base; twice daily) and narcotics for pain management. On 24 June, she was reevaluated and, because of the progression of her orf lesions, she was given intralesional injections of 3% cidofovir; her topical regimen of cidofovir was increased to 6%, as well (figure 3). One week later, the patient presented to her infectious diseases specialist with enlargement of her orf lesions, fever, and increasing pain. Weekly intralesional cidofovir injections were continued. On 19 July, she was reevaluated by her infectious diseases specialist, and her distal digit lesions were continuing to progress. Given the progression of the lesion despite surgical and medical therapy, the Centers for Disease Control and Prevention Poxvirus Program was consulted, cidofovir treatments were discontinued, and treatment with topical imiquimod 5% cream (every other day) was initiated (on 20 July). On 25 July, the patient was evaluated by her dermatologist, who noted marked improvement in all lesions. The frequency of imiquimod treatment was increased to once daily, because the patient denied local irritation. The patient continued to use imiquimod on a daily basis through 15 September. On 26 September, she was admitted to hospice because of progression of her lymphoma. At this admission, her lesions were noted to be completely resolved. In November 2005, the patient died of complications of her lymphoma, without relapse of her orf lesions.

**Discussion.** Lesions caused by orf virus usually undergo spontaneous remission within 6–10 weeks [2]. For unremitting cases of orf virus infection in humans, a number of local therapies have been applied with varying success. Excision has been used in a few cases of severe progression in patients...
undergoing immunosuppression [3]; some experts even advocate surgical excision in healthy hosts to promote rapid healing [5]. In some cases in which the underlying immunocompromise is less significant, simply eliminating treatment with immunosuppressive agents, such as corticosteroids, may be sufficient to effect a cure [6].

The pharmacologic approach to orf virus therapy in the past has focused on compounds with direct antiviral effects. Idoxuridine, a drug licensed for the treatment of herpes labialis, was used successfully to treat an immunocompetent 53-year-old female patient with a classic lesion [7]; however, this same drug was used unsuccessfully in another case report of progression in an immunocompetent 35-year-old male patient with a parapoxvirus infection [5]. Notably, the successfully treated patient received therapy within 1 week of the lesion developing, whereas therapy was delayed in the case in which treatment failure occurred. Cidofovir is a broad-spectrum antiviral agent that has shown good in vitro activity against multiple genera and species within the poxvirus family [8]. Systemic therapy using cidofovir can be complicated by nephrotoxicity, but topical therapy appears to limit this adverse effect [9]. With regard to treatment of immunosuppressed patients infected with the parapoxvirus orf, 1 case report described progressive orf virus infection in a 39-year-old renal allograft recipient. The patient was administered topical 1% cidofovir for 5 days, followed by a 5-day drug holiday, for 5 cycles; the lesion recurred 2 months later but was finally cured after another 2 cycles of therapy augmented by an occlusive dressing [9]. Systemic adverse effects (e.g., nephrotoxicity) were not observed.

Immune-modulating agents are a relatively new class of promising drugs. Although a logical choice, lesional injection of IFN-α has not proven to be effective for progressive orf virus infection [10]. However, a new addition to the immune-modulating armamentarium, imiquimod (3M), has been shown in 1 case series [11] to be effective in shortening the time to healing of orf lesions when applied twice daily for at least 5 days in relatively immunocompetent hosts. The average time to resolution in this small treatment series was 25 days, whereas evolution without treatment in previous series was 35–40 days. Furthermore, the cases demonstrated a rapid response to imiquimod (within 2–3 days) that was quite similar to ours. Imiquimod is an imidazoquinoline, which is a class of drugs that stimulate the local production of proinflammatory cytokines that, in turn, up-regulate antigen-presenting cell activity [12]. This enhanced immune surveillance promotes the skin’s innate ability to conquer infection and malignancy. To date, imiquimod has been successful in the treatment of a number of cutaneous infections, including those with viral (e.g., molluscum contagiosum, condyoma accuminata, and herpes labialis) and parasitic (e.g., leishmaniasis) etiology. Local inflammatory reactions, including erythema, erosions, and lymphadenopathy, appear to be the most common adverse events and may be severe enough to warrant discontinuation of therapy [13]. Systemic toxicity associated with imiquimod has not been noted. It is noteworthy that, although we administered imiquimod to our patient at a relatively frequent dosage (once daily), she did not experience any local symptomatologic effects; we attribute this to her generally less vigorous immune response and/or to her stoic personality.

In summary, we report, to our knowledge, the first case of progressive orf virus infection in an immunocompromised patient who was successfully treated with imiquimod; this treatment was curative, despite previous failure to promote healing with surgical debridement and cidofovir therapy. Application of imiquimod to other similar cases of orf virus infection may prevent the need for radical surgical techniques (i.e., resection or amputation) that affect the functionality and appearance of infected limbs. This case also reinforces an important public health message—namely, the potential for more severe manifestations of orf disease, a normally benign infection. Although concrete epidemiologic data is lacking, some authors suspect that orf virus infection is common among farming communities and that many individuals with cases of infection never present to health care providers [4]; therefore, the extent of disease burden is significantly underestimated. Despite this impediment, high-risk occupational groups can be easily identified. Therefore, targeted education of sheep and goat farmers, which emphasizes the use of personal protective measures—especially among farmers who are immunocompromised—may prevent the exposure of susceptible individuals to this potential health threat [1].

Figure 3. Progression of orf lesion after debridement and 2 weeks of cidofovir therapy.
Acknowledgments

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References