Milkers’ Nodules Complicated by Erythema Multiforme and Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation for Multiple Myeloma

Wendolyn R. Slattery, Mark Juckett, William A. Agger, Craig A. Radi, Teri Mitchell, and Rob Striker

Sections of 1Infectious Diseases and 2Hematology and Bone Marrow Transplant, Department of Medicine, University of Wisconsin, 3Wisconsin Veterinary Diagnostic Laboratory, and 4University of Wisconsin Hospitals and Clinics, Blood and Bone Marrow Transplant Program, Madison, and 5Section of Infectious Diseases, Gunderson Lutheran, LaCrosse, Wisconsin

We describe a case of cow-transmitted parapoxvirus infection—also known as milker’s nodules—after a hematopoietic stem cell transplantation for multiple myeloma. The infection was complicated by erythema multiforme and acute exacerbation of graft-versus-host disease. Parapoxvirus was confirmed by electron microscopy. The natural history of milker’s nodules in immunocompetent hosts is described and compared to that in our immunocompromised patient.

Milkers’ nodules, also known as paravaccinia and pseudovaccinia, are cutaneous lesions caused by infection with parapoxvirus of bovine origin [1]. In the otherwise healthy host, these nodules are relatively benign and self-limiting, but in the immunocompromised host, the outcome can be variable. We report a case of parapox infection complicated by erythema multiforme and graft-versus-host disease (GVHD) after hematopoietic stem cell transplantation (HSCT) for multiple myeloma.

Case report. A 40-year-old dairy farmer with a history of multiple myeloma underwent high-dose chemotherapy with autologous stem cell transplantation followed 3 months later by receipt of a nonmyeloablative allogeneic stem cell transplant from an HLA-identical sibling. He received cyclosporine and prednisone for GVHD prophylaxis and had an uneventful course with prompt engraftment of donor stem cells. At 110 days after transplantation, he developed grade II GVHD of the skin alone that responded promptly to treatment with prednisone (1 mg per kg of body weight).

The patient presented to the clinic 190 days after transplantation with a 1-week history of painful lesions in the mouth (diffuse erythema of his tongue, oral mucosa, and pharynx, with several small ulcers on his distal tongue and a larger ulcer on his posterior palate). In addition, he had 3 painless nodules on the dorsum of his hand (1 nodule on the right hand and 2 on the left hand) (figure 1). At the time, he was receiving hydrocortisone (1 mg per kg of body weight) and cyclosporine (1 mg per kg of body weight q.d.) administered at the end of a taper with no outward signs of GVHD of the skin, and he continued to receive acyclovir. Viral and fungal cultures of oral lesion specimens were performed at the time of presentation, and the patient was treated empirically with high-dose acyclovir and antifungals. Culture results were negative 1 week later, at which time biopsies were performed on the oral lesions.

The patient returned to the clinic 2 weeks after initial presentation. His oral lesions showed no improvement, and the results of the previously obtained biopsies of his oral lesions indicated a nonspecific inflammation. Physical examination revealed that the hand lesions had become larger. In addition, a new widespread dermatitis of targeted erythematos plaques over the patient’s trunk and arms had developed in a symmetrical distribution typical of erythema multiforme. Liver enzyme levels were elevated (aspartate aminotransferase level, 335 U/L; alanine aminotransferase level, 515 U/L; alkaline phosphatase level, 138 U/L).

Additional questioning revealed that the patient occasionally still helped on the family farm. He recalled that ~1 week before his hand lesions appeared, he had helped to retrieve a wayward calf. The calf had suckled his index finger while walking back into captivity, and he had noticed that the animal had an ulcerating lesion on the side of its mouth.

Suspecting a zoonotic infection, biopsy samples of the hand lesions were sent to the University of Wisconsin’s Veterinary Diagnostic Lab for assistance in diagnosis. Electron microscopy confirmed evidence of a parapoxvirus (figure 2).

Approximately 1 month after initial presentation with stomatitis and hand nodules, the skin rash of rounded erythematous plaques remained unchanged, and a diffuse erythema developed that resembled GVHD. In addition, the patient’s mouth discomfort increased, and liver test results continued to worsen. He was restarted on prednisone (1 mg per kg of body weight) and hydrocortisone (1 mg per kg of body weight) and continued to be treated with oral acyclovir.
Figure 1. Two rubbery-looking nodules are seen on the dorsum of the left hand of a 40-year-old dairy farmer with a history of multiple myeloma who underwent high-dose chemotherapy with autologous stem cell transplantation followed 3 months later by receipt of a nonmyeloablative allogeneic stem cell transplant from an HLA-identical sibling.

body weight) and oral triamcinolone mouth rinse. Soon thereafter, despite improvement in the oral lesions, the liver function abnormalities worsened, and the patient began to receive tacrolimus, a calcineurin inhibitor that is frequently used to inhibit engrafted, reactive T cells in cases of GVHD. The patient gradually improved, and the nodules on the hands resolved completely after ∼2 months. The parapoxvirus infection (which caused the milkers’ nodules) complicated by erythema multiforme was credited as the precipitating factor that led to acute exacerbation of GVHD.

Discussion. Infections due to the poxviruses (i.e., members of the Poxviridae family) occur in humans and animals. The parapoxviruses are morphologically distinct from the orthopoxviruses (which include smallpox, monkeypox, vaccinia, and cowpox viruses) and characteristically elicit a weak immune response by the host. Because of this, parapoxvirus lesions may be persistent and slow to heal [1].

Parapoxviruses have a worldwide distribution. They are endemic in hoofed animals (ungulates), and 3 similar species cause human infection after direct or indirect contact with infected animals. Orf virus (i.e., contagious ecthyma virus/contagious pustular dermatitis virus) is specific to sheep and goats. Our patient developed the disease after exposure to an infected cow, which could have harbored either bovine papular stomatitis virus or pseudocowpox virus (i.e., milkers’ nodule virus). They are generally considered to be occupational infections, with orf infections being the most common. Because of the clinical similarity of the diseases caused by these agents, they have been referred to collectively as farmyard pox diseases [2, 3]. The majority of human parapoxvirus infections probably go unreported, because many farmers and rural physicians are aware of the disease and make a diagnosis solely on the basis of clinical findings. No human-to-human transmission of parapoxvirus infection has been reported [2].

Bovine papular stomatitis or pseudocowpox virus is present in lesions, saliva, and nasal secretions of infected cattle. The viral particles can be stable on fomites for more than a decade, and indirect infections through knives, barbed wire, or contaminated equipment or bedding in the infected animal’s environment have been reported. The virus does, however, become inactivated after exposure to ultraviolet light [4]. Human infections can be painful, and they follow a course similar to those in cattle. Regression of lesions generally occurs without treatment within 4–6 weeks after infection. Although pseudocowpox is often confused with cowpox, there is no antigenic relationship between them (one being caused by parapoxvirus and the other by orthopoxvirus) [1].

Milkers’ nodules occur most frequently on the fingers or hands of people who have had contact with an infected cow. Following an incubation period of 3–7 days, the lesions begin as an erythematous papule, possibly with associated vesicles. This progresses over a period of weeks and forms a firm nodule that is reddish blue to brown in color. In some cases, there may also be suppurative and scabbing [5]. At this stage, the lesions may appear to be similar to those caused by cutaneous anthrax, but they lack systemic inflammation and evolve more...
slowly. The lesions eventually heal without a scar, but in cases of immunosuppression, the lesions can take months to regress, and they often recur [6].

A tentative diagnosis of the specific pox infection is often made on the basis of the host species. Definitive diagnosis may be made by isolating the virus in tissue culture or by electron microscopic identification [4]. Groves et al. [3] reported the histopathologic features of orf and milkers’ nodules in 17 patients and found no differences in dermal histological features between the 2 virus infections. In all cases, there were features typical of virus infection, with inclusion bodies and cytoplasmic and nuclear vacuolation. However, the characteristic features, taken together, were unique and unlike anything seen in other cutaneous viral lesions, such as those caused by herpes simplex, herpes zoster, molluscum contagiosum, coxsackievirus infection, or human papillomavirus infection [3].

Although the primary site of infection is a relatively benign cutaneous lesion, the secondary complication of erythema multiforme has been surprisingly well described in relation to cases of orf, particularly in Europe. Johannessen et al. [4] reported that >25% of the 60 cases of orf they observed in humans were associated with erythema multiforme. It was a frequent complication, and in the cases presented, it was the main reason for seeking medical advice. Kahn and Hutchinson [7] reported an orf infection resulting in a generalized bullous eruption that was not associated with any systemic symptoms. Wilkinson et al. [8] described a cluster of 4 cases of orf, each of which could be traced to the same infected lamb or lamb-contaminated fomites. Two of the patients they described developed widespread papulovesicular eruption of the skin and mucosa (not resembling erythema multiforme) with pyrexia, malaise, and lymphadenopathy that lasted 4–5 weeks. In Brussels, a clustering of orf cases was described that occurred during a specific 3-week period 3 years in a row [9]. Further study revealed that 44 of the cases were contracted during the time of a religious celebration in which patients were contaminated after the slaughter and manipulation of sheep with their bare hands. Erythema multiforme was a complication seen in 7 of these cases. Yirrell et al. [10] reported that erythema multiforme was induced by orf virus in 3 of 8 patients studied. None were immunocompromised.

Milkers’ nodules have been less studied. Cases have been sporadic or limited to minor epidemics [5]. In Finland, 44 cases of milkers’ nodules were recorded during the summer of 1974. Three involved morbilliform exanthema, and 7 involved erythema multiforme (2 of which were associated with bullous lesions) [11]. Hansen et al. [12] described 15 cases of milkers’ nodules in dairy farmers in Denmark that occurred during a 2-year period, including 3 cases in patients who developed an erythema multiforme–like secondary eruption.

To the best of our knowledge, milkers’ nodules have not been described in an immunocompromised host. Orf viral infections in immunocompromised humans (contracted from sheep and goats) have been reported to cause large, proliferative lesions [6]. Such infections are often mistaken for malignancy and have led to unnecessary surgery and, in some cases, amputation. Geerinck et al. [6] described a renal transplant recipient with a giant orf lesion that continued growing instead

Figure 2. Electron microscopy of parapoxvirus isolated from a biopsy specimen of a hand lesion of a 40-year-old dairy farmer with a history of multiple myeloma who underwent high-dose chemotherapy with autologous stem cell transplantation followed 3 months later by receipt of a nonmyeloablative allogeneic stem cell transplant from an HLA-identical sibling.
of regressing spontaneously. Groves et al. [3] included 2 patients in their study who were immunosuppressed. It is noteworthy that each of these cases was atypical; both patients had extremely large lesions, one of which led to amputation of the affected finger.

Viral infections are recognized triggers of GVHD. For example, cytomegalovirus viremia after HSCT is often associated with a flare-up of GVHD. In the case presented, the patient not only manifested the complication of erythema multiforme after he was infected with parapoxvirus, but the possibility exists that it also triggered chronic GVHD. Only after aggressive immune suppression with prednisone and tacrolimus did the GVHD of the mouth and the liver function test results improve.

No specific treatment exists for parapox infections. Cidofovir has broad-spectrum activity against DNA viruses, including poxviruses. It has been reported to be effective in the treatment, both topically and intravenously, of recalcitrant molluscum contagiosum and orf in the immunocompromised patient [13]. Overtreatment (perhaps as a result of misdiagnosis)—including surgical excision, antibiotics, radiation therapy, and amputation—has been reported [6]. It is notable that, despite the immunosuppressed state of the patient and the concurrent use of immunosuppressive medications in the case presented, the hand nodules resolved over the course of 2 months and did not lead to chronic infection.

The case we report here, to the best of our knowledge, the first occurrence of milkers’ nodules with erythema multiforme in an HSCT patient. Precipitation of GVHD, although never described in association with parapox, is a possibility in these circumstances, given the viral nature of the infection. As medical advances allow immunocompromised patients to live both longer and more active lives, additional atypical cases of orf or milkers’ nodules can be expected in the appropriate epidemiological setting. A proper diagnosis and an adequate knowledge base can offer preventive recommendations and spare the patient unwarranted treatments.

Acknowledgments

Financial support. RS: National Institutes of Health (grant K08 AI55750).

Potential conflicts of interest. All authors: no conflicts.

References