Orf progressiva: giant progressive and destructive infections in the immunocompromised

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Abstract

Orf virus causes a self-limited infection in humans that resolves without scarring within 6-12 weeks. However, lesions in the immunocompromised can be progressive and disfiguring. The lesions frequently recur after treatment. To our knowledge, there are eleven published cases of these infections. We propose the name orf progressiva to call attention to this progressive, treatment-resistant entity. We present a 43-year-old male ranch owner with a history of renal transplantation who contracted an orf infection from his lamb. The infection recurred despite attempts at debridement, but achieved near complete resolution after treatment with imiquimod and valacyclovir. The histologic findings of orf progressiva are identical to the early stages of classic orf infection and are characterized by epithelial hyperplasia, intracytoplasmic eosinophilic inclusions, and an edematous, vascular dermis. There is no standard treatment for orf progressiva. Surgical excision has frequently resulted in rapid reoccurrence. Topical therapies such as imiquimod and cidofovir cream in combination with excision have been successful in some cases. Acyclovir or valacyclovir with imiquimod has been reported to be effective. Two patients achieved cure with imiquimod alone. We summarize these cases to prompt recognition of orf progressiva as a distinct clinical entity that requires treatment.

Keywords: orf virus, immunocompromised

Introduction

Orf virus is a common pathogen in sheep, goats, and cattle. In these animals it causes a pustular infection of the mouth and nares called scabby mouth. The virus is transmitted to humans through contact with infected animals. Human orf is a self-limited papular infection that heals with basic wound care within 6-12 weeks [1]. In the immunocompromised, infections may be unusually large and exhibit progressive, uncontrolled growth. They do not self-resolve and can resemble giant pyogenic granuloma [1]. These lesions can recur following excision, leading to significant patient morbidity. Medical therapy has been successful in several cases, avoiding potentially mutilating surgery. We propose the term orf progressiva to describe human orf in the immunocompromised as a distinct clinical entity requiring a unique approach to diagnosis and treatment.

Case Report

A 43-year-old male ranch owner presented with an enlarging, fungating, painful mass on his right great toe. His medical history was notable for kidney transplant three years prior, managed with mycophenolate mofetil, tacrolimus, and low dose prednisone. Five months prior to presentation the pet lamb of the patient's daughter stepped on his toe while he was wearing open toed shoes, resulting in a non-healing wound. The wound was debrided, and pathology reportedly showed keloid scarring. The lesion recurred, becoming a large mass on the right hallux. A second biopsy showed granulation tissue. He was started on oral terbinafine and topical mupirocin.

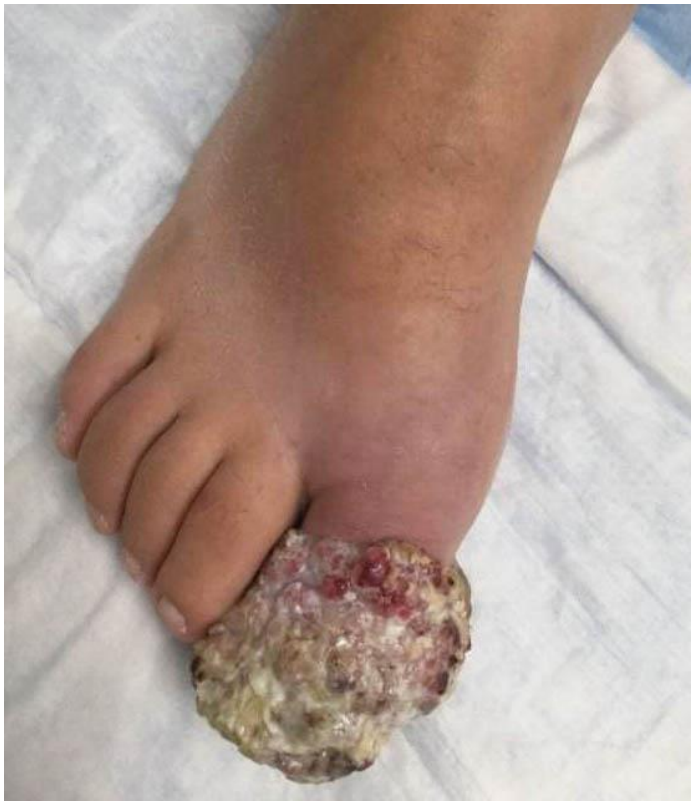

Figure 1. *Initial presentation to our institution. A large friable mass on the right hallux obscuring the toenail*

The patient was referred to our institution for a second opinion. Examination of the right hallux showed a friable fungating mass on dorsal surface extending from tip of digit to the metatarsophalangeal joint, obliterating the toenail. The border of the lesion showed substantial edema with a pseudovesicular appearance (**Figure 1**). Punch biopsy showed marked papillary dermal edema with prominent vascularity with pseudocarcinomatous epithelial hyperplasia. Eosinophilic globules suspicious for poxviral inclusions were noted (**Figure 2**). Tissue stains were negative for fungal or mycobacterial pathogens. Wound cultures grew *Pseudomonas aeruginosa*. The paraffin block was submitted to the Centers for Disease Control, where their review of the pathology slides and immunohistochemistry was negative for viral inclusions of orf. PCR, however, was positive for orf. The patient was started on topical imiquimod and oral valacyclovir. He received a two-week course of ciprofloxacin for the pseudomonal superinfection. At last follow up after 4.5 months of treatment, the lesion had reached near complete resolution (**Figure 3**).

Review

Orf virus (ORFV) is a parapoxvirus within the family of poxviruses, which are double stranded DNA viruses that infect humans and animals. Orf virus is believed to have a predilection for the keratinocyte, within which it evades host immune responses. The virus expresses an IL10 analog that reduces cytokine synthesis, decreasing immune cell recruitment to infected tissues [1]. It also expresses pro-apoptotic proteins that result in programmed death of monocytes and macrophages. Viral VEGF stimulates epidermal hyperplasia, capillary neogenesis, and increased vascular permeability, which contribute to the classic highly vascular lesions [2].

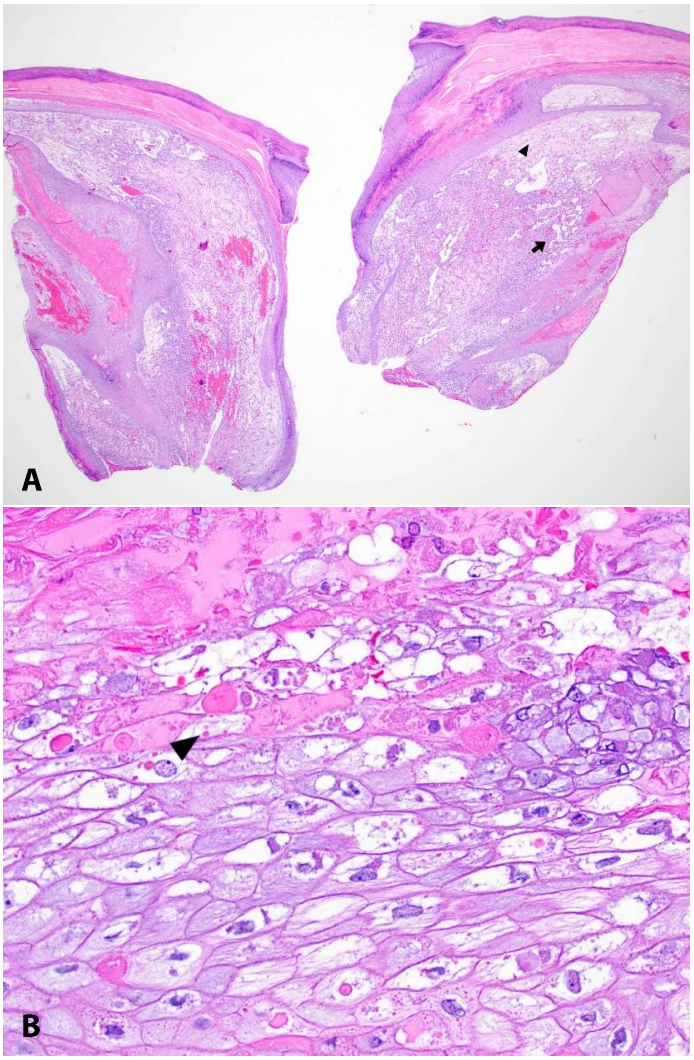

Figure 2. *H&E staining of the biopsy specimen.* ***A****) On low magnification, there is papillary dermal edema (arrowhead) and dense irregular vascularity (arrow).* ***B****) On higher magnification, eosinophilic intracellular inclusions are visualized (arrowhead).*

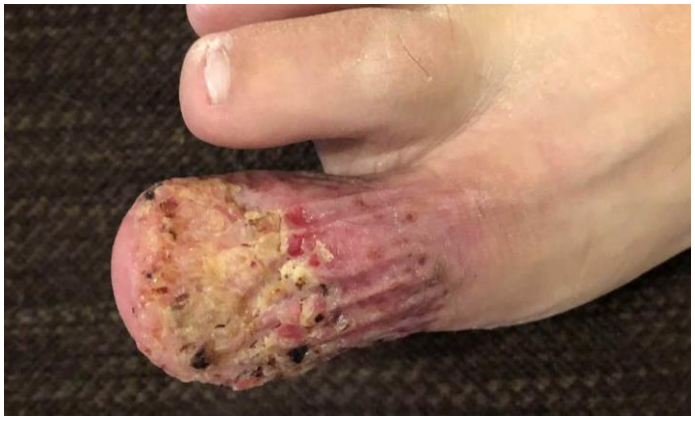

Figure 3. *Right hallux after two months and 4.5 months' treatment with valacyclovir and imiquimod. At 4.5 months, there is a residual erythematous nodule at the first interphalangeal joint. The nail plate is once again visible.*

Orf virus is found ubiquitously in cattle, sheep, and goats. In these animals it causes ecthyma contagiosum (also known as scabby mouth or infectious pustular dermatosis). This manifests clinically as pustular lesions on the mouth, hooves, teats, and nostrils that eventually scab over [2]. Contact with active lesions on these animals or contact with fomites are the most common methods of transmission to humans. As such, human orf is an occupational dermatosis seen among farmers, ranchers, and animal health care workers [1]. Rarely, human to human transmission can occur. Human orf infection has a three- to seven-day incubation period, after which a painless solitary papule appears. Patients may also experience low grade fever and lymphadenopathy. Lesions progress through six clinical stages (**Table 1**) before regressing without scarring in 6-12 weeks [1]. Infection is suspected in patients with an appropriate history of exposure to livestock and a supporting physical examination. Electron microscopy has been used to confirm diagnosis, but cannot distinguish between parapoxviruses [3]. Histology is another useful diagnostic technique. More recently, diagnosis is established by conventional PCR or reverse-transcription PCR of lesional tissue, which is more accurate [1].

Histopathology

In the early stages of human orf infection, there is intracellular epithelial edema (ballooning degeneration) and vacuolization of the keratinocytes in the upper epidermis with eosinophilic intracytoplasmic inclusions. There is epithelial hyperplasia and an edematous vascular dermis [4,5]. In the targetoid stage, a mixed inflammatory infiltrate of plasma cells, histiocytes, lymphocytes, and macrophages develops. The rete ridges are thin

Table 1. *Six stages of human Orf infection with clinical and histologic features [4]. Orf progressiva is characterized by uncontrolled growth and does not self-resolve. The histologic features are identical to the early stages of classic orf.*

Clinical Stage	Timeline	Features	Histologic Findings
Stage 1: Maculopapular	3-7 days	Erythematous papule	Vacuolization of cells in superficial epidermis. Intracellular eosinophilic inclusions
Stage 2: Targetoid	7-14 days	Pink central papule, surrounded by a white ring, bordered by an erythematous rim	Red center: pyknotic epidermal cells White ring: vacuolated epidermal cells with eosinophilic intracellular inclusions Red halo: dilated blood vessels; infiltrate of histiocytes, lymphocytes, plasma cells
Stage 3: Acute	14-21 days	Draining nodule	Reticular degeneration of the epidermis with loculated vesicles Epidermal loss in some areas Dilated hair follicles surrounded by pyknotic cells Inflammatory dermal infiltrate of histiocytes, macrophages, lymphocytes
Stage 4: Regenerative	21-28 days	Firm nodule with yellow crust and punctate black dots	Extrusion of follicle cells onto the epidermal surface Epidermal regeneration
Stage 5: Papillomatous	28-35 days	Nodule develops a papillomatous surface	Epidermis develops finger-like downward projections
Stage 6: Regressive	>35 days	Nodule regresses with formation of a dry crust. Eventually heals without scarring	Reduction in acanthosis and inflammatory infiltrate

and elongated. Ballooning degeneration eventuates in reticular degeneration and further vesiculation of the epidermis. Pyknotic cells plug hair follicles and are later eliminated. In the final regressive stage, the epidermis regenerates with resolution of the epithelial hyperplasia and inflammation (**Table 1**).

Orf virus shares histologic features with many other conditions, most of which are viral. Cowpox and smallpox lesions are histologically identical to orf virus and may show similar or identical eosinophilic inclusions on H&E; electron microscopy or PCR can be used to distinguish between them [5]. Pyogenic granulomas are distinguished by the presence of an epidermal collarette and a predominantly neutrophilic infiltrate. The lesions of herpes simplex, varicella, and zoster are differentiated by the presence of multinucleated giant cells and intranuclear inclusions.

Orf progressiva

Immunosuppressed patients, such as those with solid organ transplant or lymphoma, can present with more severe or multifocal infections that do not self-resolve and are recalcitrant to treatment. Published cases that we have classified as orf progressiva are detailed in **Table 2**. Many of these patients are on glucocorticoids, cyclosporine, mycophenolate, or tacrolimus at the time of infection. Treatment-resistant human orf infection has also occurred in a patient on etanercept for psoriatic arthritis [6]. A similar progressive presentation has been reported in an immunocompetent patient [3]. Orf progressiva starts as a nodule that rapidly progresses to become vascular and friable, much like a pyogenic granuloma. Lesions as large as 9cm have been reported [7]. Thus, this presentation appears to be a distinct clinical entity.

The lesions of orf progressiva are histologically identical to the early lesions of classic human orf. They are characterized by marked epithelial hyperplasia with ballooning and reticular degeneration. Eosinophilic intracytoplasmic inclusions and a vascular, edematous dermis are present. Histopathologic features of orf infection are summarized in **Table 1**.

Treatment

Surgical excision of orf progressiva lesions can be followed by rapid recurrence [6-9]. In one patient, a giant tumor on the hand was excised twice with skin grafting before cure was ultimately achieved with a combination of systemic interferon, a third excision, and hypochlorite dressings [7]. Giant orf lesions have been mistaken for skin cancers, leading to amputation [10]. Intentional amputation of affected digits has also been reported and was curative [11]. Treatment with topical or intralesional interferon alpha, cidofovir, acyclovir, and imiquimod often in combination have been reported with success.

Acyclovir is an inhibitor of viral DNA polymerase and is effective in treating herpesvirus infections [12]. Imiquimod is an agonist of toll-like receptor 7, a component of the innate immune system that activates Langerhans cells. It is often used for treatment of viral warts, molluscum, and cutaneous malignancies [13]. There are two cases of successful treatment of orf progressiva with imiquimod alone [8,13]. Interferon alpha is an antiviral that increases macrophage and lymphocyte activity and decreases viral VEGF activity, which is especially effective in vascular tumors. Cidofovir is a nucleotide analogue that was developed for treatment of cytomegalovirus, but interestingly is effective against resistant DNA viral infections and HPV-associated lesions [14]. In this case, we combined valacyclovir to theoretically inhibit viral replication and imiquimod to upregulate the patient's own immune system and made progress in treating the patient's infection.

Discussion

Orf in the immunocompromised represents a distinct, treatment-resistant entity characterized by rapid uncontrolled growth. We propose the name orf progressiva to describe its destructive nature and its failure to self-resolve. To our knowledge, there is only one published case of an immunocompetent patient presenting with orf progressiva [3]. Infected patients report traumatic contact with sheep, via occupation or through preparation of meat. This leads to an aggressive pyogenic-granuloma-like tumor that

recurs despite attempts at surgical removal. The histology shows epithelial hyperplasia, intracellular viral inclusions, and prominent dermal vasculature. These findings are somewhat nonspecific and diagnosis via histopathology is difficult. Diagnosis with PCR is definitive. It is important to culture the tissue as bacterial superinfection is relatively common and can be treated with appropriate antibiotics [10].

Our patient's infection was treated with a combination of imiquimod and valacyclovir. It is unclear to what extent valacyclovir was effective in treatment of the infection as it specifically targets herpesvirus DNA polymerase. One published case successfully utilized acyclovir in combination with interferon alpha [15]. This raises the question of whether monotherapy with imiquimod in our case or interferon alpha in the other would have been sufficient for cure, especially as there are two case reports of successful treatment with topical imiquimod alone [13,15]. Determining to what extent valacyclovir and acyclovir are active against orf virus will require further research.

Conclusion

We have compiled these cases to prompt clinicians to recognize orf progressiva as a distinct, treatment-resistant entity. This infection should be suspected in immunocompromised individuals who present with a friable mass and report occupational or recreational contact with livestock. However, this presentation can also occur in the immunocompetent, though this has been reported only once [3]. To our knowledge, there is only one case of orf progressiva that was successfully treated with a single excision [16]. All other patients have required serial excision, imiquimod, or combination therapy for cure of the condition. A few patients have suffered amputation of the affected digit. Recognition of this entity should allow for a trial of medical therapy, in an attempt to avoid the morbidity and high recurrence associated with surgical removal.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 2. *Published cases that we have classified as progressiva, with clinical course and histologic features.*

Date of publication	Patient Demographics	Comorbidities	Immunosuppressive Agents	Clinical Features	Histologic Findings	Treatment Course	Complications	Outcome
Savage et al. 1972 [11]	65M finger cut while cleaning sheep head	Lymphoma	Cyclophosphamide, vincristine, prednisone	Left middle finger 5cm x 3cm, 5 weeks	Fingerlike epithelial projections. Vacuolization of epidermis with Intracytoplasmic eosinophilic inclusions. Pyogenic granuloma-like vascular changes in the dermis.	Amputation of the digit	Loss of digit	Resolution after amputation
Tan et al. 1991 [7]	30M sheep farmer	Nezelof Syndrome	n/a	Right ulnar hand 9cm x 8.5cm, 6 weeks R dorsal hand 1cm x 1 cm, 2 weeks Left middle finger, 2 weeks (8 years later)	Pseudoepitheliomatous hyperplasia. Edematous vascular dermis	Excision w/ skin graft x2 Excision w/ skin graft x2 Excision. Excision followed by 40% Idoxuridine and interferon alpha	Recurrence after excision	A, B: Full resolution after third excision C. Full resolution after third excision, subcutaneous interferon, sodium hypochlorite
Degraeve et al. 1999 [9]	48M knife cut while cutting mutton	Kidney transplant	Cyclosporine, azathioprine, corticosteroids	Left thumb, 7 days	Epidermis with intracellular edema, ballooning degeneration and reticular degeneration. Dermis with dense lymphocytic and neutrophilic infiltrate	Surgical excision × 2	Recurrence after excision	Resolution after eight weekly cryotherapy sessions
Geerinck et al. 2001 [17]	39F contact with slaughtered sheep	Kidney transplant	Cyclosporine, methylprednisolone, mycophenolate mofetil	Left fourth finger 3cm, 6 weeks	Intraepidermal eosinophilic Inclusions and reticular degeneration	Cidofovir cream 5 days alternating with povidone iodine ointment 5 days; repeated for 7 weeks	Recurrence	Resolution after cidofovir for 5 days under occlusion, followed by 9 days rest, repeated x1

Ballanger et al. 2006 [16]	31M sheep and rabbit breeder	Cystic fibrosis s/p heart and lung transplant	Tacrolimus, mycophenolate mofetil, prednisone	Right hand 7cm x 5cm x 4cm, 2 weeks Left cheek 3.5cm x 2.5cm, 2 weeks	Acanthosis with ballooning degeneration and intracellular eosinophilic inclusions. Edematous granulation tissue with prominent vascularity	A,B: excision		Resolution after excision
Key et al. 2007 [3]	41M farmer, bottle fed newborn lambs	Otherwise healthy	n/a	Right cheek 5cm	"Florid" inflammatory reactive changes	Ciproxime. Cephalexin. Curettage and cautery. PDL x2 with amoxicillin-clavulanate	Recurrence with satellite lesions	Curettage with cautery followed by doxycycline
Lederman 2007 [13]	73F farm worker, bottle-fed baby goats with crusting on nose and mouth	Non-Hodgkin Lympho-ma; rheumatoid arthritis	Fludarabine, rituximab	Left thumb x2 right forearm, 3 weeks	Keratinocytes with spongiform degeneration, ballooning degeneration and eosinophilic cytoplasmic inclusions, irregularly shaped nuclei. Increased vascularity	A, B Doxycycline followed by cephalexin. Excision of lesions. IV vancomycin. Cidofovir 3% cream. Intralesional 3% cidofovir weekly with topical 6% cidofovir	Progression of all lesions	Resolution after 2 months daily 5% imiquimo d cream
Zaharia et al. 2010 [15]	61M contact with slaugh-tered sheep	Kidney transplant	Prednisolone, mycophenolate mofetil, cyclosporine	Right forefinger, 5 weeks	Ulcer with necrosis of the upper epidermis. Eosinophilic cytoplasmic inclusions within vacuolated epidermal keratinocytes. Edematous granulation tissue with prominent vascularity	Prednisone and mycophen olate mofetil decreased. Imiquimod uptitrated to bid x6 weeks		Lesion resolved 12 weeks later
Rordam et al. 2013 [6]	45M sheep farmer	Psoriatic arthritis	Etanercept	Right temple 7cm, 3 months Left third finger, 3 months	Vacuolization of epidermal cells.	Etanercept stopped A, B: Shave removal and cryotherapy	A,B Recurrence after excision	Resolution after 17 weeks of daily imiquimo d with q3 week cryotherapy

Ran et al. 2015 [18]	40s M, worked with livestock	Solid organ transplant	tacrolimus	Left thumb 2x3cm, 3 months Left forearm 3cm x 5cm, 3 months Right forefin-ger, 3 months	Acanthosis, ballooning degeneration, and eosinophilic inclusions in keratinocytes. Vascular dermis	A, B, C: Oral acyclovir 400mg q6hr for 9 weeks and intralesional interferon alpha 1.5 million IU/week for 6 weeks		Resolution after 6 weeks.
Ertekin, et al. 2017 [19]	68M, close contact with slaughtered lamb during religious ceremony	CLL in remission	n/a	Left thumb 4 weeks; 2 cm	Pseudoepithelio-matous hyperplasia, severe capillary proliferation. keratinocytes with ballooning degeneration and eosinophilic cytoplasmic inclusions	Excision at 10 weeks. Imiquimod 5% cream 3x weekly with valacyclovir 1g tid, stopped after 6 weeks due to progression. Imiquimod 5% 3x weekly with intralesional interferon alpha weekly, stopped due to pain	Recurrence after excision. Progression despite valacyclovir and imiquimod	Systemic subcutaneous interferon alfa-2a 2x weekly with imiquimod 3x weekly. Resolution after 6 weeks
Harms et al. 2019 [8]	48M, finger cut while cooking lamb	Liver transplant	Mycophenolate mofetil Tacrolimus	Left third finger, 6 weeks	Pseudoepithelio-matous hyperplasia, ballooning degeneration. Intracytoplasmic eosinophilic inclusions; Edematous dermis with prominent vascularity	Shave removal x2	Small area of recurrence after second shave removal	Resolution with imiquimod
Opene et al. 2020 (current case)	43M, ranch owner. Lamb stepped on toe while wearing sandals	Renal transplant	Mycophenolate mofetil, tacrolimus	Right hallux, 5 months	Epithelial hyperplasia. Intracellular eosinophilic inclusions. Papillary dermal edema and vascularity	Debridement x2	Recurrence after debridement	Resolution with imiquimod twice daily, valacyclovir daily

All cases except Key et al. [3] occurred in setting of immunocompromised state. All were characterized by uncontrolled growth; none of the infections self-resolved.