Severe Monkeypox Infection of the Eye and Periocular Region

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Case Report

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Abstract

Background: Monkeypox is an emerging zoonotic infection with potentially severe ocular and periocular consequences, particularly in immunocompromised patients.

Case Presentation: Two cases of monkeypox presenting in patients with AIDS are described. In the first case confluent lesions resulted in orbital compartment syndrome and total eyelid necrosis. In the second case eyelid involvement was accompanied by corneal melt and perforation. Despite aggressive treatment both patients developed permanent loss of vision and, in one case, death.

Conclusions: Many cases of ocular or periocular monkeypox are mild and self-limiting. In immunocompromised patients more severe disease may manifest and requires systemic as well as local ophthalmologic treatment.

Background

Monkeypox (mpox) is an emerging zoonotic viral infection with potential for fulminant disease involving the eye and periorbital region. First described in humans in Africa in 1970, the virus had been predominantly limited to isolated outbreaks in central and west Africa (particularly Democratic Republic of Congo) until 2003 when it was first encountered in America after importation of infected rodents from Ghana led to at least 70 cases. Since that time outbreaks have occurred in several countries with no prior history of the disease, though these have generally been limited in scale and associated with travel to endemic regions of Africa.

The current global outbreak is unprecedented, both in case volume and geographic distribution. Cases began to rise significantly in July 2021 and, in the US, appear to have peaked in July-August 2022. With a peak of approximately 500 daily cases, there have now been nearly 30,000 cases in the US at the time of writing and around 80,000 globally. While cases have decreased dramatically since their peak, the disease has not been eliminated and the ultimate outcome (potential endemicity) in the US is unclear. It is currently believed that human-to-human transmission alone cannot sustain mpox in the human population and a zoonotic reservoir with primary animal-to-human transmission may be required.

Human to human transmission is via respiratory droplets or contact with infected persons skin lesions or body fluids.

Mpox has a variable incubation period of up to 21 days and symptoms typically last two to five weeks. Active disease is characterized by a febrile prodrome of one to five days followed by the sudden onset of vesicular-pustular lesions and, in some cases, lymphadenopathy. The lesions may present in varying stages simultaneously and generally involve the face, trunk, hands and feet in a centrifugal pattern. As the lesions resolve they develop crusts which then flake away leaving a scar. Mucus membranes and the eye may be involved. Ocular manifestation typically presents as conjunctivitis but in severe cases may progress to keratitis and corneal ulceration with permanent vision loss.
Diagnosis is often suspected on a clinical basis in patients presenting with characteristic lesions but may be confirmed with serologic confirmation of IgM anti-monkeypox antibodies or with PCR amplification of viral DNA from lesional swabs. Treatment with the antiviral tecovirimat is available under an Expanded Access Investigational New Drug protocol for patients with severe disease or at risk for severe disease.\(^6,7\) Initially developed for the treatment of smallpox, tecovirimat targets viral envelop protein and prevents virus from leaving infected cells. Preexposure vaccination is recommended for at risk individuals and likely reduces infection risk and severity although human data is lacking.\(^8\) Vaccination may also be used post-exposure in an effort to reduce the severity of infection.\(^9\)

The vast majority of cases are mild and self-limited and do not require hospitalization or leave long-term sequela. However, significant morbidity and even mortality is known to occur, particularly in immunocompromised individuals.\(^10\) The current report documents two cases of disseminated mpox with fulminant ocular and periocular manifestations resulting in devastating sequela and vision loss.

**Case 1**

A 41-year-old male with past medical history of HIV/AIDS (viral load 8800 copies/mL and CD4 count 53 cell/mm\(^3\)) and chronic hepatitis B infection presented as a transfer to the burn unit for management of disseminated lesions involving the extremities, trunk and face including the eyelids in the setting of severe mpox infection. The patient had a history of HIV with poor adherence with anti-retroviral therapy (ART) for two years preceding presentation.

The patient reported that he had participated in unprotected anal receptive intercourse with a male partner and one week later developed rectal pain. One week after the onset of pain he noted the onset of lesions on his extremities, face and oral mucosa one week later which prompted his presentation to a local clinic. Mpox infection was suspected based on this history and the characteristic lesion appearance. Serologies confirmed the diagnosis at which point a two-week course of oral tecovirimat (600 mg by mouth twice daily) was initiated. Re-initiation of ART was recommended with combination bictegravir-emtricitabine-tenofovir and darunavir-cobicistat but the patient reported difficulty in obtaining the medication for financial reasons.

A week after completion of tecovirimat treatment, the patient presented to an outside hospital with new and worsening facial lesions accompanied by bilateral eyelid swelling. The patient was admitted for intravenous tecovirimat (200 mg twice daily) as well as ART but continued to develop new facial and body lesions as well as progressive facial edema. A maxillofacial CT was significant for bilateral pre-septal edema without post-septal extension as well as subcutaneous soft tissue edema of the head and neck. Ophthalmology was consulted due to the development of severe right periorbital swelling. Visual acuity was 20/40 and 20/25 in the right and left eye with no rAPD and normal intraocular pressures. External examination was notable for coalescent, exquisitely tender lesions on an erythematous and edematous right upper and lower eyelid and nearly complete mechanical ptosis. The left eyelids were less affected but demonstrated similar lesions. Anterior and non-dilated fundus exams were unremarkable in
both eyes. The patient was started on empiric therapy with linezolid and ceftriaxone out of concern for possible superinfection of his disseminated skin lesions. He was also started on topical trifluridine eye drops every four hours as preventative therapy against corneal or conjunctival mpox involvement.

A week following admission the patient received vaccinia IVIG (6000 units/kg) due to progression of disease. In order to treat progressive swelling and out of concern for possible immune reconstitution inflammatory syndrome he received a week-long course of dexamethasone. By this point, the right eye had progressed to complete mechanical ptosis with the necrotic vesicles and bullae coalescing to form a diffuse eschar of his right face from the hairline to the submental area. Examination of the right eye was not possible due to an inability to open the eyelids or visualize the globe. The left periorbital region exhibited worsening edema but manual retraction of his left eyelids was possible. In the left eye, near visual acuity was 20/20 and his anterior segment exam was normal.

The patient’s edema and pain progressively worsened and he was transferred to the intensive care unit and underwent tracheostomy and mechanical ventilation for epiglottic and supraglottic edema complicated by respiratory distress. After a month-long admission at the outside hospital the progression of necrotic lesions of much of the right face prompted transfer to the adult burn unit of the authors’ institution for sub-specialty care.

On arrival to the burn unit, ophthalmologic exam revealed firm eyelids which were unable to be opened with Desmarres retractors under sedation due to extremely rigid eschar. (Fig. 1a) He also demonstrated marked edema of the left eyelids. A repeat maxillofacial CT was obtained showing severe and diffuse soft tissue swelling involving the right scalp, face, and neck (Fig. 2); however, no post-septal extension of inflammatory changes was evident. The extensive right periorbital eschar prompted concern for possible orbital compartment syndrome and surgical debridement of the right upper and lower eyelids with attempted lateral canthotomy and cantholysis was performed on the right. Tangential excision the upper and lower eyelid exhibited full-thickness necrosis deep to the septum. (Fig. 1b). Despite these interventions the right eyelids could not be opened adequately for examination or visualization of the globe due to the tissue rigidity and swelling.

Biopsies obtained from the right eyelid were positive for orthopoxvirus DNA suggesting active viral replication despite greater than 6 weeks of tecovirimat therapy. Histologic examination of lesions on the leg demonstrated full-thickness epidermal necrosis with diffuse ballooning degeneration of keratinocytes and multinucleated keratinocytes. The dermis exhibited a mild perivascular inflammatory infiltrate and there was thrombosis of superficial vasculature, findings consistent with prior reports. Bacterial culture of debrided right facial tissue was also positive for multiple bacterial organisms, including pan-sensitive pseudomonas aeruginosa, extended spectrum beta-lactamase escherichia coli and corynebacterium striatum and the patient was continued on IV vancomycin and meropenem. Mycobacterial and fungal cultures as well as herpetic viral PCR were negative. CT of the head and face demonstrated thrombosis of the facial artery suggesting that the patient’s extensive facial necrosis was a result of vessel thrombosis or obliteration secondary to viral-induced inflammation.
Additional debridement of the face and sacrum were scheduled but the patient acutely developed profound pancytopenia and he was deemed no longer to be a surgical candidate. No significant improvement in the lesions of the trunk and extremities was observed and facial necrosis extended to include the entirety of his face. After extensive discussion the patient was continued on antimicrobial therapy but developed increasing requirements for pressor support and mechanical ventilation at which point family members consented to a transition to comfort focused care. Three weeks following arrival at the burn intensive care unit and twelve weeks following initial presentation with mpox the patient expired due to overwhelming sepsis.

Case 2

A 47-year-old male with a past medical history of HIV (viral load 4,830 copies/mL, CD4 count 28 cells/mm$^3$) not on ART and syphilis (previously treated) presented to our institution with a report of left eye vision loss. The patient had been diagnosed with mpox four weeks prior to presentation and had been treated on an outpatient basis with a two-week course of tecovirimat and an over-the-counter skin care regimen. The day of presentation he developed generalized weakness and altered mental status prompting a roommate to call emergency services.

On presentation the patient demonstrated disseminated skin lesions characteristic for mpox including lesions of the left eyelids including the lid margin. (Fig. 3) Vital signs were largely within normal limits with only mild tachycardia and no fever. Ophthalmologic exam was notable for opacification of the left cornea and uveal prolapse through an inferior corneal perforation with hand motions vision. Fundoscopy was not possible on the affected left side but appositional choroidal detachments were evident on b-scan ultrasound. The right cornea and anterior segment were normal in appearance and there were no fundoscopic abnormalities or evidence of cytomegalovirus (CMV) retinitis.

Laboratory evaluation was notable for leukocytosis and blood cultures demonstrated gram positive cocci in chains. He also was noted to have an elevated creatinine and potassium suggestive of acute kidney injury. The patient also tested positive CMV (viral load 74,000); testing for cryptococcus and histoplasmosis was negative. Corneal gram stain and culture grew group C/G streptococcus but were negative for fungal elements.

He was treated promptly with tecovirimat and combination bictegravir/emtricitabine/tenofovir. Cefepime and vancomycin were administered for the treatment of bacteremia. Cidofovir was initiated after the finding of CMV viremia and he received vaccinia IVIG. Topical moxifloxacin eye drops were administered every two hours in addition to trifluridine eye drops administered four times daily. He was also administered IV fluids for his acute kidney injury.

No significant improvement in the patient's cutaneous or ocular disease was noted despite these interventions although he remained hemodynamically stable. On hospital day two the patient was brought to the operating room for tectonic corneal grafting and debridement of the eyelid lesions. (Fig. 4)
Biopsies of the eyelid skin demonstrated findings consistent with prior reports of mpox including full thickness necrosis, ballooning degeneration and multinucleated epithelial cells. (Fig. 5a,b). In the conjunctiva, cells with cytoplasmic inclusions morphologically consistent with virus were present in the stroma (Fig. 5c,d).\(^1^2\)

The patient was subsequently transferred to the burn unit for additional debridement of his extremities and perineum. At two weeks post debridement and corneal transplant the patient demonstrated no light perception vision with an intact donor cornea. Treatment is on-going at the time of publication.

**Discussion**

Ocular and periocular mpox infection has been described in limited case reports and series.\(^1^3\) These reports include case of conjunctivitis\(^5^,\(^1^4^–^1^7\) (with or without follicles), keratitis\(^5\) and periocular skin involvement\(^5^,\(^1^5^,\(^1^7\). However, most involvement in the reported cases is mild without long-term sequela. Severe ocular manifestations in America and Europe are exceedingly rare, although cases of corneal transplant and blindness have been reported in historical African outbreaks with corneal ulceration in as many as 4% of unvaccinated patients.\(^1^8\)

The presented cases of mpox are notable as the most severe ocular and periocular involvement reported in the developed world to date. Both patients were HIV positive and suffering from AIDS with CD4 counts less than 200 cells/mm\(^3\). This profound immunocompromise is likely contributory for the dramatic disease manifestations in these patients. The observed predilection of mpox infection for men who have sex with men in the current outbreak is concerning because of this group’s historically higher rates of HIV infection placing these patients at risk for severe disease and poor outcomes.\(^1^9^,\(^2^0\)

In the presented cases, as well as in historical case series, mpox lesions appear to have a predilection for the eyelid margin compared with non-marginal eyelid skin.\(^1^8\) The lesions observed in the second case are reminiscent of the blepharoconjunctivitis reported in herpes simplex infection.\(^2^1\) Tropism of this type, for the mucocutaneous junction, is not limited to the herpes simplex virus and is also well recognized in human papillomavirus.\(^2^2^,\(^2^3\) While the lesions observed in these patients were necrotizing, their distribution differed notably from the necrosis in bacterial necrotizing fasciitis which is observed to spare the lid margin in the literature and in the authors’ experience.\(^2^4\) Margin involvement is uncommon in necrotizing fasciitis due to the robust blood supply from the marginal arterial arcade but this does not appear to be protective in mpox. Whether margin involvement increases the likelihood of conjunctival and corneal disease or is a result of inoculation from primarily involved ocular tissues is an open question.

Orbital compartment syndrome has not previously been described as a complication of mpox. Most frequently encountered in the setting of traumatic orbital hemorrhage, orbital compartment syndrome is also a recognized complication of severe burns.\(^2^5\) Orbital compartment syndrome in the setting of burn has been frequently attributed to fluid shifts from volume resuscitation but may occur in the absence of
aggressive volume resuscitation as well. The etiology of the orbital compartment syndrome encountered in the first case was not conclusively determined but possibly represents multifactorial eyelid and orbital edema from significant IV fluid administration, immune reconstitution inflammatory syndrome and mpox infection. The orbital volume was unable to expand because of the extremely rigid eyelid eschar overlying the orbital aperture resulting in compartment syndrome.

Management of orbital compartment syndrome generally centers on orbital decompression with lateral canthotomy and cantholysis. The patient’s multifaceted infection and tenuous status prevented more aggressive surgical intervention or adjuvant therapy with medications such as mannitol.

Management of periocular and ocular mpox is limited by a lack of high-quality evidence. Supportive care with lubricating drops and ointments is reasonable for mild cases of conjunctivitis. In more severe cases or when corneal involvement is evident systemic therapy should be initiated with tecovirimat. Additional systemic therapies include, vaccination vaccinia IVIG Local treatment of ocular involvement is reported with trifluridine which shows in vitro activity against orthopoxviruses. While debridement of necrotic tissue is reasonable to prevent bacterial superinfection it is not likely to prevent disease progression and is not a mainstay of therapy.

These cases of periocular and ocular mpox infection help define the spectrum of disease manifestations. Immunosuppressed patients are at risk for fulminant necrotizing disease and corneal perforation and systemic therapy with tecovirimat and vaccinia IVIG should be implemented. Early assessment by ophthalmologists may help determine whether there is a role for topical treatment with trifluridine. Periocular involvement does not require debridement in all cases but careful attention must be paid to lid mobility and intraocular pressure in order to ensure that an orbital compartment syndrome has not developed. Human mpox infection has greatly increased in prevalence globally since its first description in the 1970s physicians of all disciplines should be aware of this entity and its potentially devastating consequences.

Declarations

Ethics Approval: This report was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication: Informed consent was obtained from all subjects and/or their legal guardian(s) for publication of identifying information/images in an online open-access publication.

Availability of data: Not applicable

Competing interests: The authors declare they have no competing interests.

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References


Figures

Figure 1

(a) External photograph of the patient’s face on presentation with extensive necrosis of the right face and complete ptosis. Characteristic mpox lesions are visible on the left side and along the margin of necrotic tissue. (b) Appearance following tangential excision of the left eyelids with deep tissue non-viable in appearance. Canthotomy and cantholysis was also performed but the eyelids remain firmly closed.
Figure 2

Contrast enhanced axial CT scan of the face showing significant soft tissue swelling and thickening of the right eyelids. There is an absence of contrast enhancing vessels on the right compared to the left consistent with vaso-occlusive disease.
Figure 3

Mpox lesions of the patient’s (a) hand, (b) lower extremity and (c) eye. Note upper margin involvement and erosion of the lateral canthus.
Figure 4

External photograph of the left periocular region following debridement. Remaining tissue appears viable with a bleeding base.
Figure 5

Eyelid skin showed acute and chronic inflammation with necrosis and ballooning degeneration of epithelium (a); rare multinucleated cells are also present (b, arrow). In the conjunctiva, changes were most prominent in the stroma with mixed inflammation and scattered enlarged cells with eosinophilic cytoplasmic inclusions (c,d, arrows).