Monkeypox Virus and Ophthalmology—A Primer on the 2022 Monkeypox Outbreak and Monkeypox-Related Ophthalmic Disease

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IMPORTANCE An ongoing global monkeypox virus outbreak in 2022 includes the US and other nonendemic countries. Monkeypox ophthalmic manifestations may present to the ophthalmologist, or the ophthalmologist may be involved in comanagement. This narrative review creates a primer for the ophthalmologist of clinically relevant information regarding monkeypox, its ophthalmic manifestations, and the 2022 outbreak.

OBSERVATIONS Monkeypox virus is an Orthopoxvirus (genus includes variola [smallpox] and vaccinia [smallpox vaccine]). The 2022 outbreak is of clade II (historically named West African clade), specifically subclade IIb. In addition to historic transmission patterns (skin lesions, bodily fluids, respiratory droplets), sexual transmission has also been theorized in the current outbreak due to disproportionate occurrence in men who have sex with men. Monkeypox causes a characteristic skin eruption and mucosal lesions and may cause ophthalmic disease. Monkeypox-related ophthalmic disease (MPXROD) includes a spectrum of ocular pathologies including eyelid/periorbital skin lesions, blepharoconjunctivitis, and keratitis). Smallpox vaccination may reduce MPXROD occurrence. MPXROD seems to be rarer in the 2022 outbreaks than in historical outbreaks. MPXROD may result in corneal scarring and blindness. Historical management strategies for MPXROD include lubrication and prevention/management of bacterial superinfection in monkeypox keratitis. Case reports and in vitro data for trifluridine in other orthopoxviruses suggest a possible role for MPXROD. Tecovirimat, cidovir, brincidofovir and vaccinia immune globulin intravenous may be used for systemic infection. There is a theoretical risk for monkeypox transmission by corneal transplantation, and the Eye Bank Association of America has provided guidance. Smallpox vaccines (JYNNEOS [Bavarian Nordic] and ACAM2000 [Emergent Product Development Gaithersburg Inc]) provide immunity against monkeypox.

CONCLUSIONS AND RELEVANCE The ophthalmologist may play an important role in the diagnosis and management of monkeypox. MPXROD may be associated with severe ocular and visual morbidity. As the current outbreak evolves, up-to-date guidance from public health organizations and professional societies are critical.

The intent of this article is to aggregate from an ophthalmic standpoint what is presently known about monkeypox from historical outbreaks and the emerging 2022 outbreak. Because of the restricted focus of this primer, we direct the reader for additional reading to recent Viewpoint pieces published in JAMA, recent review articles, and formal guidance from public health organizations and professional societies.

Virology in Brief

Monkeypox virus (MPXV) is an enveloped double-stranded DNA virus and member of the genus Orthopoxvirus, which also includes variola virus (the cause of smallpox), vaccinia virus (from which modern smallpox vaccines are derived), and cowpox virus. The virus was named for initial identification in monkeys, but the reservoir species is thought...
to be an unknown rodent species (possibly Gambian pocketed rats, rope squirrels, or other rodents) rather than monkeys. MPXV is divided into clades, which were historically named based on geographic associations but have recently been renamed by the WHO to reduce stigma and discrimination. Clade I (formerly Congo Basin clade) has historically caused more severe disease. Clade II (formerly West African clade) is further subdivided into 2 subclades, clade IIa and clade IIb. The incubation period of MPXV is typically 7 to 14 days but may be up to 21 days.

Clinical Presentation of Human Monkeypox Infection

MPXV infection typically begins with a prodromal fever, followed 2 to 3 days later by skin and oropharyngeal/mucosal eruptions. Oropharyngeal/mucosal lesions may precede skin lesions. The skin eruptions may have a centrifugal distribution (greater density of lesions on face and extremities). In the 2022 outbreak, skin lesions most commonly occur in the anogenital region, which is affected in up to 73% of patients. Lymphadenopathy may be an important clinical feature, which may distinguish the rash from that of smallpox. The number of skin lesions may be quite variable, ranging from fewer than 25 to more than 500 lesions. The skin lesions may follow a characteristic sequence of stages: macular, papular, vesicular, pustular, and then crusting and sloughing. An important feature in distinguishing the monkeypox rash from that of chicken pox is that for a paroxysmal eruption, the characteristic skin rash may occur on the face, monkeypox lesions may occur on the periorbita and eyelids; eyelid margin lesions occurring in association with conjunctivitis have been reported; in such co-occurrences it is not clear if the conjunctival lesions occur secondary to regional autoinoculation from the eyelid margin lesions or if the eyelid and conjunctival lesions are both due to regional eruption. Monkeypox conjunctivitis may include a conjunctival follicular reaction, discrete vesicular or papular conjunctival lesions, conjunctival ulceration, pseudomembranes, and/or subconjunctival nodules. In the 2010 to 2013 outbreak of clade I in the Democratic Republic of the Congo, patients with conjunctivitis had higher rates of systemic symptoms (nausea, fatigue, lymphadenopathy, chills/sweating) and of being "bedridden". Corneal disease in the setting of monkeypox can include ulcerative keratitis, immune stromal keratitis, and neurotrophic keratitis and may result in corneal scarring and bacterial superinfection. Thus, MPXROD may be associated with severe ocular and visual morbidity including central corneal scarring, visual impairment, the need for corneal transplant, and phthisis bulbi. Persistent MPXROD may occur as late as 6 weeks from monkeypox onset and can be severe. Moreover, recrudescence of corneal disease and visual shedding was reported in a 2003 clade I keratitis case.

Diverse additional ophthalmic manifestations (including iritis/iritis, retinitis/chorioretinitis, optic neuritis, ophthalmoplegia, and dacyrocystitis) have also been described in smallpox (variola) infection and after smallpox vaccination (with vaccinia). However, these presentations have never been reported as MPXROD, and it remains unknown if they can occur in human monkeypox infection. A comprehensive review of the ophthalmic manifestations of smallpox infection and smallpox vaccination by Semb previously reported that the data about MPXROD in the current 2022 outbreak are emerging. In a retrospective analysis between April 27 and June 24, 2022, of 528 cases from 43 sites in 16 countries, patients had a history of travel (most frequently to Europe) in the month preceding symptom onset. High rates of concomitant infection with HIV/AIDS have been reported. Historical data have shown that children are at increased risk for severe disease, but given the current rarity in children, the spectrum of pediatric disease in the current outbreak is incompletely characterized. Epidemiologic differences in the current outbreak (such as the predominance in MSM and rare pediatric occurrence) in comparison with previous outbreaks have been noted, and differences in the spectrum of ocular manifestations and frequency of ocular disease may also emerge.

Ocular findings may include external (periocular and lid) and ocular surface lesions (blepharoconjunctivitis and keratitis). As the characteristic skin rash may occur on the face, monkeypox lesions may occur on the periorbita and eyelids. Eyelid margin lesions occurring in association with conjunctivitis have been reported; in such co-occurrences it is not clear if the conjunctival lesions occur secondary to regional autoinoculation from the eyelid margin lesions or if the eyelid and conjunctival lesions are both due to regional eruption. Monkeypox conjunctivitis may include a conjunctival follicular reaction, discrete vesicular or papular conjunctival lesions, conjunctival ulceration, pseudomembranes, and/or subconjunctival nodules. In the 2010 to 2013 outbreak of clade I in the Democratic Republic of the Congo, patients with conjunctivitis had higher rates of systemic symptoms (nausea, fatigue, lymphadenopathy, chills/sweating) and of being "bedridden". Corneal disease in the setting of monkeypox can include ulcerative keratitis, immune stromal keratitis, and neurotrophic keratitis and may result in corneal scarring and bacterial superinfection. Thus, MPXROD may be associated with severe ocular and visual morbidity including central corneal scarring, visual impairment, the need for corneal transplant, and phthisis bulbi. Persistent MPXROD may occur as late as 6 weeks from monkeypox onset and can be severe. Moreover, recrudescence of corneal disease and visual shedding was reported in a 2003 clade I keratitis case.

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patients infected with clade I, with similar rates in smallpox-vaccinated vs smallpox-unvaccinated patients. Historical data have suggested that smallpox vaccination may reduce the burden of ocular disease in monkeypox cases: analysis of the 1981 to 1986 clade I outbreak in the Congo Basin reported conjunctivitis and blepharitis in 30% of smallpox-unvaccinated vs 7% of smallpox-vaccinated persons. The effect of vaccination on rates of MPXROD in the current outbreak is unknown.

Diagnosis

The diagnosis of monkeypox begins with a high index of clinical suspicion, and diagnosis can be challenging, as atypical rash presentations may resemble chickenpox/zoster, syphilitic eruptions, and other poxvirus infection. The US Centers for Disease Control and Prevention (CDC) has provided case definitions for the 2022 monkeypox outbreak. A “suspect” case is any patient with characteristic rash and/or clinical suspicion for monkeypox with compatible epidemiologic features. A “probable” case is a patient without other known Orthopoxvirus exposure (including from infection) who is positive for Orthopoxvirus DNA by polymerase chain reaction, Orthopoxvirus immunohistochemistry, or electron microscopy or is positive for anti-Orthopoxvirus IgM within 4 to 56 days from rash onset. A “confirmed” case is a patient with demonstration of MPXV DNA on polymerase chain reaction test results or isolation of MPXV in culture. The CDC provides instructions for reporting cases.

As of September 6, 2022, in the US initial laboratory testing of specimens for Orthopoxvirus occurs at Laboratory Response Network laboratories or authorized commercial laboratories; subsequently, further characterization of the specimen may occur at the CDC. Laboratory specimen collection guidance from the CDC is presently for collection of skin lesion samples. In case reports of patients with monkeypox with conjunctivitis and skin lesions, swabs sent from both skin and the conjunctiva demonstrated similar viral load on polymerase chain reaction test results. However, collection of specimens from lesions on the ocular surface (conjunctival or corneal) or other mucosal sites has not yet been recommended. Specimens submitted can be dry swabs, swabs in viral transport media, or lesion crusts. Two swabs should be collected from a single lesion and processed together, and it may be prudent to separately sample additional lesion(s) from different parts of the body or which are different in appearance. Swabs should be synthetic (eg, Dacron, polyester, or nylon). The swab can be obtained from the surface of the lesion; it is not necessary to unroof the lesion. The swab/specimen should be placed whole in a sterile container with gasket seal, or the end of the swab should be broken off into a 1.5- or 2-mL screw-capped tube with O-ring. Specimens should be collected, stored, and shipped refrigerated or frozen. The reader should refer to the CDC for additional guidance, as recommendations regarding collection and processing of specimens may change.

Treatment

As the course of infection with MPXV is typically self-limited, the management of systemic monkeypox infection is frequently supportive. Antiviral agents (tecovirimat, cidofovir, brincidofovir, and vaccinia immune globulin intravenous [VIGIV]) may be used for the systemic treatment of monkeypox in patients with severe disease or who are considered at risk for severe disease. There are limited available data about the efficacy of systemic antiviral agents for monkeypox in general, and data regarding MPXROD are especially limited.

Tecovirimat, which inhibits the product of the Orthopoxvirus F13L gene, is presently the monkeypox antiviral agent used most widely in the US. Tecovirimat received US Food and Drug Administration (FDA) approval in 2018 for treatment of smallpox based largely on animal data, and the CDC has a non-research-expanded access Investigational New Drug protocol for its use as empirical treatment of nonvariola Orthopoxvirus infections, including monkeypox. Of note, the eye is currently considered a “special hazard” anatomic site; therefore, ocular involvement in human monkeypox infection can be an indication for tecovirimat. However, ophthalmic bioavailability and efficacy of tecovirimat for MPXROD are not yet well characterized.

Cidofovir, a DNA nucleotide analog that inhibits viral DNA polymerase, is FDA approved for the treatment of cytomegalovirus retinitis and has been shown in vitro and in animal models to have activity against orthopoxviruses, including MPXV. Brincidofovir, a prodrug of cidofovir, has also been shown to be efficacious against Orthopoxvirus species in vitro and in animal models and was approved by the FDA for treatment of smallpox in 2021. VIGIV is FDA approved for complications of vaccinia vaccination and may be used for the treatment of other orthopoxviruses by an expanded-access protocol. VIGIV is FDA approved for complications of vaccinia keratitis and is presently the monkeypox antiviral agent used most widely for monkeypox keratitis. Treatment with VIGIV was associated with increased corneal scarring, but subsequent studies have not replicated this association. Although the presence of keratitis does not appear to be an absolute contraindication for VIGIV, the CDC advises caution if VIGIV is used in MPX with active keratitis.

There is no available topical ophthalmic antiviral agent specific for monkeypox infection. Trifluridine, 1%, ophthalmic solution, approved by the FDA for ocular herpes simplex keratitis, has been used in case reports of ocular vaccinia and has been shown in vitro to have activity against orthopoxviruses. The efficacy of trifluridine specifically in human MPXROD has not yet been reported. Historically, the management of MPXROD and ocular manifestations of other Orthopoxvirus infection have relied on generous topical lubrication, and this remains an important component of supportive ophthalmic therapy for MPXROD. Topical antibiotics for corneal ulceration and epithelial defects may be important to prevent bacterial superinfection.

Transmission and Prevention

Transmission may occur both between humans and from animals to humans (including by scratch, bite, and bushmeat ingestion). Transmission may occur by contact with skin lesions, bodily fluids, or respi-
Corneal Transplantation: Possible Risk for Transmission

Presently, there are no reported cases of monkeypox transmission by corneal transplant. However, as noted previously, patients with active monkeypox conjunctivitis can shed virus.21,23,25,27,31 Global rates of monkeypox are historically low in high-income countries where corneal transplantation is much more frequent; therefore, an outbreak of monkeypox in high-income countries presents a novel scenario. To minimize potential transmission in the use of cadaveric corneal grafts, in July 2022, the Eye Bank Association of America provided precautionary recommendations.57 Based on the MPXV incubation period of 5 to 21 days, the Eye Bank Association of America has recommended exclusion of donors who in the preceding 21 days exhibited (1) MPXV positivity, (2) unexplained Orthopoxvirus positivity, (3) rash concerning for monkeypox, or (4) close contact with a monkeypox case.57 Cornea specialists should continue to watch for further guidance from the Eye Bank Association of America as the outbreak progresses.

Vaccination

There is presently no monkeypox-specific vaccine, but smallpox vaccination may provide up to 85% cross-protection against monkeypox.3 However, smallpox vaccination has not been routinely performed in the US since the 1970s due to smallpox eradication.58 Also, it is unclear to what extent a smallpox vaccination administered decades earlier might provide against monkeypox. As noted previously, earlier outbreak data have suggested that vaccination is associated with lower rates of MPXROD.28 It is unknown whether extended time from earlier vaccination might result in diminishment of this association.

Smallpox vaccination is currently being used to reduce transmission of monkeypox. There are presently 2 available smallpox vaccines: ACAM2000 (Emergent Product Development Gaithersburg Inc) and JYNNEOS (Bavarian Nordic). ACAM2000 contains replication-competent vaccinia virus and is administered by skin scarification.2 JYNNEOS contains the replication-impaired modified Ankara vaccinia strain and is administered subcutaneously in 2 doses.2 Neither vaccine is generally available routinely to the public, except for preexposure prophylaxis in select groups with heightened occupational risk (laboratory personnel working with orthopoxviruses, research workers handling orthopoxviruses, and certain healthcare and public health workers designated by public health authorities) or for postexposure prophylaxis.3,59 Clinicians should continue to monitor vaccination guidelines as eligibility expands based on availability and the evolution of the outbreak. The availability of JYNNEOS is increasing, and up-to-date distribution information is available through local public health organizations.50

Conclusions

MPXROD may occur in human monkeypox infection and rarely leads to severe corneal sequelae. Ophthalmologists can play an important role in detecting cases and reducing visual morbidity associated with the disease. Clinical and public health recommendations regarding monkeypox continue to evolve as the outbreak progresses. Improved understanding of disease process, preventive strategies, and treatment options will help to determine optimal therapeutic and public health strategies. Clinicians should be watchful for updated guidance on monkeypox from the CDC and the WHO.
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