The Ocular Surface

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Monkeypox and Ocular Implications in Humans

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Monkeypox is a viral zoonotic infection with some characteristics bearing resemblance to smallpox. Monkeypox was first isolated in Denmark in the late 1950s from a colony of laboratory monkeys used for polio virus research, and first identified as a cause of disease in humans in the 1970s in the Democratic Republic of the Congo.[1] The current outbreak could be related to the loss of vaccine-derived immunity following the discontinuation of routine smallpox vaccination, which offered previous cross-protection against monkeypox and reduced human-to-human transmission. In 2022, there was a new global outbreak of monkeypox infection, first reported in Europe in May 2022.[2] It has since spread to more than 50 countries across five regions, with more than 3000 cases of monkeypox infections being reported. On July 23, 2022, the World Health Organization declared the outbreak of monkeypox as an international public health emergency.

Monkeypox is a DNA virus in the same orthopox genus as variola, the causative agent of smallpox, with two distinct genetic clades, the clade 1 (the former Congo basin/Central African clade), and clade 2 (the former West African clade).[3] The current global outbreak in 2022 which was first brought to attention in Europe and North America is related to Clade 2 outbreak of monkeypox, with the possibility of the circulating virus undergoing accelerated genetic mutation and human adaption. Both animal-to-human and human-to-human transmission can occur. In animal-to-human transmission, the virus is transferred through contact with an infected animal's bodily fluid or bite. The extent of viral circulation in animal populations and the precise species harboring the virus is not certain, but several lines of evidence suggest rodents as a likely reservoir for the virus.

Monkeypox is usually a self-limited disease with a course ranging from two to four weeks.[1] The virus, like smallpox, sets in with a febrile prodrome period followed by the appearance of enanthem and then exanthema in centrifugal distribution. However, several differences can distinguish the classic presentation of the two diseases: presence of lymphadenopathy in monkeypox; parenteral modes of infection in monkeypox in animal models, such as transdermal and mucocutaneous routes; and lower efficiency of human-to-human transmission in monkeypox.[1]

In classic monkeypox, the prodrome period typically lasts up to five days and consists of fevers, chills and myalgia. There may also be intense headache, lymphadenopathy, and severe fatigue. The hallmark of monkeypox is its disseminated vesiculo-pustular rash, which lasts up to two to three weeks. The rash begins as macules, which then evolve to papules, vesicles, then pustules, with crusting over. Lesions are well circumscribed, deep, and often develop umbilication, and may be painful and/or itchy. Complications from the virus include secondary skin infection, bronchopneumonia, sepsis, gastroenteritis, and encephalitis.[5]

In the 21st century, we have witnessed multiple emerging infectious diseases with ophthalmic presentations including Zika, Ebola, SARS-CoV-2, and now, monkeypox. There are multiple lines of evidence suggesting that monkeypox affects the eye, with ophthalmic manifestations that are common and easily identified. However, what is less clear is how the ocular infection arises, be it primarily or via direct inoculation.

The characteristic rash of monkeypox often involves the peri-orbital and orbital skin.[4] In a study of the clinical features of 282 patients with monkeypox, conjunctivitis and edema of the eyelids were common and caused considerable but temporary distress.[5] 17% of unvaccinated and 13% of patients vaccinated for smallpox had focal lesions on the conjunctiva and along the eyelid margin. In another study, conjunctivitis tended to be more readily observed in young children <10 years.[6] Blepharitis was observed in 30% of unvaccinated and 7% of previously vaccinated against smallpox.[7] In terms of source of infection, conjunctivitis was more common among patients affected by monkeypox from an animal source at 20.3% as compared to those affected by monkeypox from a human source at 16.4%.[8] In another study on the concomitant symptoms associated with ophthalmic presentation, it was found that patients who had conjunctivitis also had a higher frequency of symptoms such as nausea, chills, oral ulcers, sore throat, general malaise, lymphadenopathy, and photophobia.[6] Patients may also present with frontal headache involving the orbital region.[9]

One of the most devastating consequences of monkeypox infection is keratitis, corneal scarring and resultant loss of vision. Bacterial superinfection of corneal ulcerations may result in severe complications such as corneal perforation, anterior staphyloma, and phthisis bulbi, leading to irreversible blindness.[10] In a previous study, unilateral or bilateral blindness, along with reduced vision, were noted in 10% of primary infections and 5% of secondary infections.[8]

Ocular symptoms such as conjunctivitis may also be used as a prognostic factor predicting the course of the disease.[6] Patients with conjunctivitis report more severe symptoms such as being “bed-bound” as compared to patients without ocular manifestations. There have been numerous incidents of monkeypox with ophthalmic manifestations in the medical literature. **Figure 1** (*courtesy: Professor Andre Curi*) illustrate lid lesion and ocular surface involvement (peripheral keratitis and conjunctivitis) in patients with monkeypox infection. All three patients had positive PCR for monkeypox from conjunctival swabs.

Steps may be taken to protect the vision of at-risk patients by the application of topical lubricants to prevent abrasions against the ocular surface and vitamin supplementation to boost overall immunity. This staves off secondary bacterial infection of the cornea that tends to occur later on with the disease progression. Off-label use of trifluridine or vidarabine eye drops, known to be useful in the treatment of Orthopox-virus associated corneal lesions, can be applied every four hours for seven to ten days.[10]

Of note, it has been demonstrated that severe ocular sequelae and complications of monkeypox are more common among populations unvaccinated against smallpox at 74% as compared to patients who have been vaccinated at 39.5%.[5] Hence, the ability of smallpox vaccination to offer cross-protection against monkeypox must be highlighted, with nation-wide vaccine campaigns being implemented in endemic areas and offered to high-risk groups. To this end, education of the public about both the disease and the concept of vaccine immunity is of critical importance, to promote uptake and acceptance of smallpox vaccination if necessary.

At present, there is no licensed treatment available for human monkeypox. Only two orally bioavailable drugs, brincidofovir and tecovirimat, have been approved by the FDA for the treatment of smallpox and have demonstrated efficacy in orthopoxviruses, including monkeypox, in animal models. However, neither drug has been studied in human efficacy trials.

Recognizing the link between monkeypox and ocular manifestations is the first step in managing ocular complications with the potential for vision loss in patients affected by the disease, given prior reports of blindness due to corneal complications. As physicians and healthcare workers become more familiar with the ophthalmic presentations of monkeypox, the disease can potentially be recognized more easily in its early stages, enabling suitable and timely treatment of symptoms. Given the rising epidemic of monkeypox and the possibility of further outbreaks, it is prudent for ophthalmologists to consider monkeypox as part of their differential diagnosis when they encounter patients presenting with ophthalmic symptoms like conjunctivitis, blepharitis, keratitis, or corneal abrasions, looking for concomitant symptoms of monkeypox such as a disseminated vesiculo-pustular rash, along with a febrile prodrome and lymphadenopathy.

The ongoing 2022 wave of monkeypox across multiple countries in the world is the largest in history to occur outside of Africa, and the virus continues to pose a threat to humans with significant potential to cause future outbreaks. Further evaluation and research are required to understand the interplay of factors involved in its continued propagation. Establishing evidence-based case management strategies is key to enable epidemic preparedness, as stated by the Integrated Disease Surveillance and Response Technical Guidelines released by the World Health Organization and Centers for Disease Control.

Understanding the clinical course of the disease and features predictive of poorer outcomes will further allow patient prioritization and optimization of resource allocation. Research from observational studies and interventional animal experiments will continue to inform vaccine and drug development, improving patient management and treatment. Familiarity with the epidemiology of the disease, sources of infection and routes of transmission will allow for better management and response by public health institutions in the event of another epidemic, as well as help to prevent future outbreaks.

Monkeypox can have significant effects on multiple organ systems, disrupting the protective barrier of skin and mucosal surfaces and commonly affecting the eye. Given prior outbreaks in which patients with monkeypox developed ophthalmic manifestations leading to corneal scarring, ocular symptoms should be recognized by physicians and other healthcare workers promptly to ensure appropriate management. Increasing surveillance and detection of monkeypox cases with ophthalmic manifestations is essential for better understanding the evolving nature of this resurging disease. A multidisciplinary team involving veterinarians, physicians, virologists, and public health experts will be ideal to develop comprehensive and holistic solutions to tackle the ongoing monkeypox pandemic.

Figure Legends:

Figure 1: Patient # 1 (A) diagnosed with Monkeypox presenting with vesicle on the left upper eyelid (yellow arrow). Patient had positive reverse transcriptase-polymerase chain reaction (RT-PCR) for Monkeypox from the skin lesions and conjunctiva. HIV positive patient (patient # 2) (B) with the diagnosis of Monkeypox infection presenting with peripheral keratitis (blue arrows). Reverse transcriptase-polymerase chain reaction (RT-PCR) was positive for Monkeypox from conjunctival swab. HIV positive patient (patient # 3) (C) with the diagnosis of Monkeypox infection with hyperemic conjunctiva and serous discharge. Reverse transcriptase-polymerase chain reaction (RT-PCR) was positive for Monkeypox from conjunctival swab.

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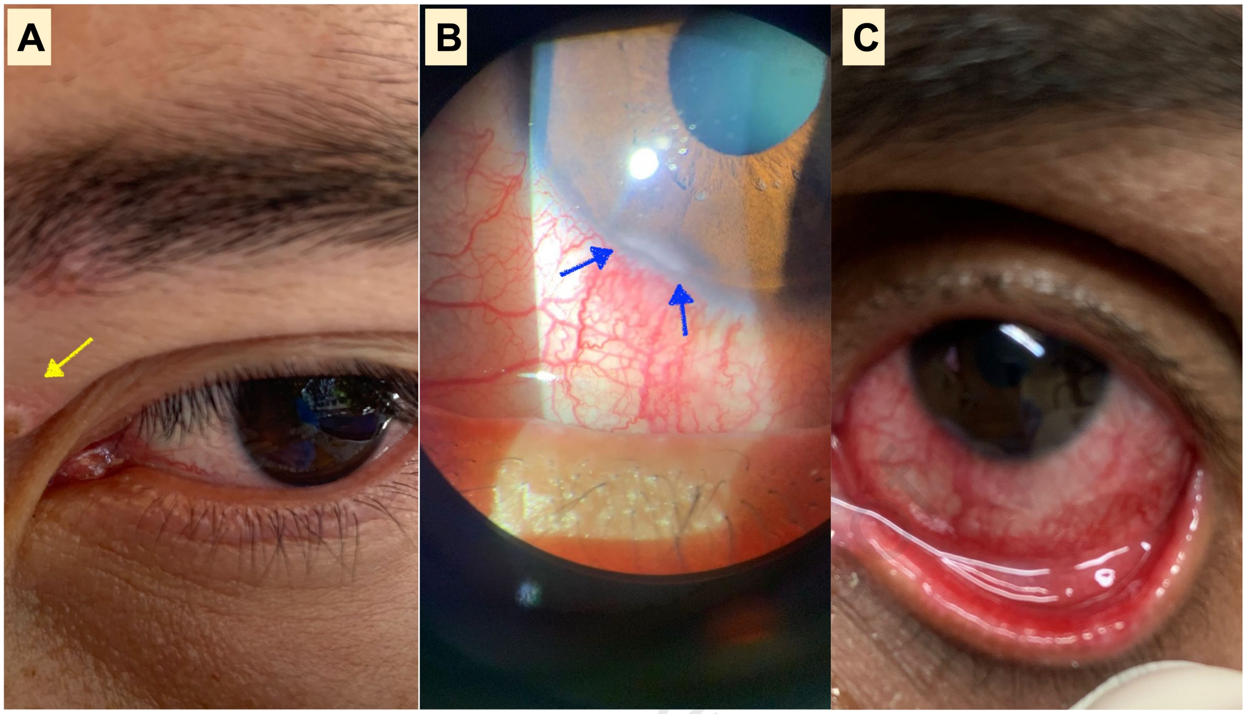
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