REVIEW



A Review of Monkeypox Ocular Manifestations and Complications: Insights for the 2022 Outbreak

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ABSTRACT

Monkeypox (MPVX) infection has been associated with multiorgan presentations. Thus, monkeypox infection's early and late complications are of particular concern, prompting health systems to decipher threatening sequels and their possible countermeasures. The current article will review the clinical signs and symptoms of the present and former outbreaks, differential diagnoses, workup and treatment of the ocular manifestations of MPXV infection in detail. One of the uncommon yet considerable

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K. Hassanpour (🖂) Ophthalmic Research Center, Research Institute for Ophthalmology and Vision Science, Shahid Beheshti University of Medical Sciences, Paidarfard St, Bostaan 9th St, Pasdaran, Tehran 16666, Iran e-mail: kiana.hassanpour@gmail.com MPXV complications is ocular involvement. These injuries are classified as (1) more frequent and benign lesions and (2) less common and vision-threatening sequels. Conjunctivitis, blepharitis and photophobia are the most uncomplicated reported presentations. Moreover, MPXV can manifest as eye redness, frontal headache, orbital and peri-ocular rashes, lacrimation and ocular discharge, subconjunctival nodules and, less frequently, as keratitis, corneal ulceration, opacification, perforation and blindness. The ocular manifestations have been less frequent and arguably less severe within the current outbreak. Despite the possibility of underestimation, the emerging evifrom observational investigations dence documented rates of around 1% for ocular involvement in the current outbreak compared to a 9-23% incidence in previous outbreaks in the endemic countries. The history of smallpox immunization is a protective factor against these complications. Despite a lack of definite and established treatment, simple therapies like regular lubrication and prophylactic use of topical antibiotics may be considered for MPXV ocular complications. Timely administration of specific antivirals may also be effective in severe cases. Monkeypox usually has mild to moderate severity and a self-limited course. However, timely recognition and proper management of the disease could reduce the risk of permanent ocular sequelae and disease morbidity.

Keywords: Monkeypox; Ocular manifestations; Blepharoconjunctivitis; Keratitis; Corneal opacification; Blindness; Smallpox vaccination

Key Summary Points

The ocular manifestations of monkeypox are uncommon and encompass a spectrum of symptoms from eyelid/ periorbital lesions, blepharoconjunctivitis and keratitis to corneal scarring and blindness.

The ocular involvement in the ongoing outbreak seems to be rarer and to cause fewer permanent sequels compared to historical outbreaks.

While there is no definite treatment for ocular manifestations, oral tecovirimat is the mainstay of options, and trifluridine eye drops, antibiotics, steroids, vitamins and other antivirals may be effective.

Due to a higher risk for more severe complications in unvaccinated individuals, encouraging high-risk populations to take vaccines through promoting public awareness is of great importance.

INTRODUCTION

Monkeypox virus (MPXV) is an etiological agent of zoonotic disease endemic to central and West Africa [1]. Considered a high-consequence infectious disease (HCID) [2], it presents as a smallpox-like disease with cutaneous rashes and fever but with substantially lower mortality [3]. Since the termination of the worldwide smallpox vaccination program in the 1970s, several outbreaks of increasing scale have occurred in endemic areas [4, 5]. The first evidence of MPXV presence in non-African countries dates back to the US cases in 2003, where the virus spillover occurred from infected mammals [6, 7]. Since then, multiple countries

outside Africa have reported cases linked with endemic areas. Even though the virus dissemination predominantly occurs via human-toanimal exposure, it could also spread between humans [8]. It is known that the virus is transmitted mainly through contact with body fluids, skin lesions, respiratory droplets and contaminated clothing of infected individuals [9].

The 2022 MPXV outbreak in non-endemic countries has puzzled scientists around the world regarding the possibility of containing the outbreak and unusual transmission in the population of men who have sex with men (MSM). This multi-country outbreak initiated in the UK has spread to more than 50 countries predominantly in Europe [10]. Current disease manifestations are rather atypical compared to previous outbreaks, including anogenital rashes and milder prodrome. Therefore, it has been proposed that the case definition should be revised as we are becoming more vigilant about virus behavior [11, 12].

It is imperative for ophthalmologists to be familiar with the ocular manifestations of MPXV disease. Therefore, the present review discusses all reported ocular manifestations to date.

OCULAR SYMPTOMS OF MONKEYPOX

Methods and Literature Search

We conducted a comprehensive search in online databases of PubMed and Scopus using the key terms related to: [monkeypox, monkeypox virus, 'monkey pox', MPXV] AND [eyelid, blepharitis, palpebral, lacrimal, corneal, keratitis, keratopathy, conjunctivitis, uveal, uveitis, scleritis, episcleritis, iritis, iridocyclitis, planitis', choroiditis, chorioretinitis, 'pars retinitis, papillitis, retinal, dacryoadenitis, cataract, glaucoma, endophthalmitis, orbital, optic, ocular, eye, peri-ocular, intraocular, photophobia, ophthalmic, visual, blindness]. No restrictions of language or record types were applied. This article is based on previously conducted studies and does not contain any

new studies with human participants or animals performed by any of the authors.

General Manifestations

As the illness progresses toward different stages. the infection affects multiple organs and anatomical sites. The typical disease manifestation begins with viral prodrome that lasts 2--3 days and predominantly with fever and, to a lesser extent, other constitutional symptoms, including asthenia, headache, myalgia, lymphadenopathy, chills and sweats [3, 13]. The presence of lymphadenopathy discriminates against other differential diagnoses, including smallpox [14, 15]. After prodromal resolution, these symptoms are replaced by maculopapular rashes in centrifugal patterns with different stages of evolution and could affect mucosal membranes and ocular surfaces. However, in the 2022 clusters of infections, the rashes are appearing on sites (anogenital regions) linked to sexually transmitted diseases (STDs) and possibly raise this concern for MPXV [11, 16]. Moreover, the atypical signs of rash initiation before fever and short-lived or absent prodrome phase in some cases could imply that the current outbreak requires more advanced surveillance for case definition and categorizing patients with different clinical suspicions [11].

Besides the acute phase of the disease that typically lasts 2–4 weeks, the viral infection could contribute to prolonged disease or longterm complications, particularly in vulnerable groups with compromised immune systems. These sequels consist of bronchopneumonia, encephalitis, ocular surface involvements and secondary bacterial infections imposed on primary lesions [17, 18].

Ocular Complications

The 2022 Monkeypox Outbreak

As the current outbreak continues, less common ocular manifestations are being reported worldwide; still, the scale of the outbreak has not reached a sufficient point to conduct robust investigations on the evolution of rare symptoms. Regarding the present outbreak, these ophthalmic complications have been rarely (< 1%) [19] reported in the cases from 27 EU/ EEA countries (> 20,000 cases as of 27 September 2022), while this profile has been higher in the endemic countries varying from 9 to 23% [20]. Other studies in the current outbreak reported a quite similar incidence of MPXV ocular complications, 2 out of 197 cases in London (1%) [21], 2 out of 185 cases in Spain (1.1%) [22] and 2 out of 264 cases in France (0.8%) [23].

One of the first documentations of ocular involvement in the recent outbreak dates to a case series performed in international cases from April to June 2022 across 16 countries. Among 528 subjects, three patients had conjunctival lesions, which led to hospitalization in two of them [24]. In line with this study, a case series on 264 subjects from France reported ocular involvement in two patients who were hospitalized afterward, considering ocular involvement a severe form of the disease [25]. The ocular manifestations, treatments received and ultimate picture of the MPXV-infected cases during the 2022 outbreak are summarized in Table 1.

Previous Outbreaks

Human Studies The MPXV ophthalmic involvement may vary from subtle to sightthreatening symptoms. The most frequent and uncomplicated ocular manifestations are blepharitis and conjunctivitis [18, 26]. Patients with conjunctivitis encountered a higher frequency of constitutional symptoms and light sensitivity and had a higher tendency to become bedridden (47%) compared to those without (17%) [27]. It could imply that conjunctivitis might be associated with more severe forms of the disease and a predictor of the disease course. Moreover, the investigation of the 2003 US outbreak as the first document of MPXV in the western hemisphere reported blepharitis in 9% of patients who had direct exposure to infected pets [7]. Preauricular lymphadenopathy and frontal headache affecting orbits have also been reported [20].

The protective effect of smallpox vaccination for MPXV corneal lesions is reflected in World Health Organization (WHO) enhanced

| Table 1 (|)cular man | ifestations, | management and outcome of monkeypo: | x during the | 2022 outbreak | | | |
|----------------------------------|-------------|---|---|---|---|--|---|------------|
| Type of investigation | Country | Age and sex | Ocular complications | Ocular PCR test for Monkeypox DNA | Systemic treatments | Ocular treatments | Outcome | References |
| Case report | Cameroon | 14-year-old male | Bilateral eye redness, conjunctival injections and no discharge | NR | Oral cloxacillin 500 mg | Tetracycline 1% eye ointment | Symptoms resolved after 7 days with no complication | [57] |
| Case report | US | 36-year-old female | Left eye redness, discomfort and subconjunctival and left upper cyelid umbilicated nodules | NR | Oral nonsteroidal anti- inflammatory (NSAIDs) | Topical phenylephrine | Significant improvement in the follow-up period | [58] |
| Case report | Spain | 42-year-old male | Left eye pain, photophobia and lacrimation Left eyelid margin lesions with discharge and conjunctival whitish infiltrative lesion and thickness No corneal lesions or intraocular inflammation | Positive on conjunctival swabs | Systemic tecovirimat 600 mg and acyclovir 1 g | Ocular drops, including chlorhexidine 0.2%, povidone-iodine 1%, ganciclovir 0.15% and moxifloxacin | Conjunctival pseudomembranes developed in the second week of treatment. Lesion excision and fluorometholone were initiated, and lesions were resolved after 4 weeks | [63] |
| Case report | Italy | 35-year-old male | Right eye pain and photophobia Over 10 umbilicated papules in the tarsal and bulbar conjunctiva, temporal limbus and fornix | Positive in conjunctival swabs | IV cidofovir 5 mg/kg | NR | Ocular lesions resolved after 3 days of treatment | [59] |
| Observational cohort study | France | 10 patients with ocular symptoms | Two had ocular impairments requiring hospitalization. One had minor palpebral lesions, and the other had blepharoconjunctivitis with severe keratitis | NR | IV cidofovir 5 mg/kg and oral valaciclovir | Ocular dexamethasone, ganciclovir, tobramycin | The case with keratitis did not show full resolution of symptoms during the hospital stay | [25] |
| Case report | Italy | 26-year-old male | Multiple papular lesions in the right eyelid with progressive conjunctival and peri-orbital involvement deteriorating into more lesions in the upper and lower eyelids and the formix, periorbital edema and conjunctival hyperemia | Positive in both eyelid and conjunctival swabs | Intravenous cidofovir (5 mg/kg weekly) and oral probenecid | Topical steroid therapy anti-inflammatory and vitamin A-based eye drops | Asynchronous recession of the lesions and a total disappearance approximately 2 months after the onset of the symptoms | [56] |
| Case report | Switzerland | 39-year-old male | Right eye itchiness and redness Conjunctival follicular reaction Small white vesicles present on the nasal bulbar conjunctiva | Positive in conjunctival swabs | NR | NR | NR | [64] |
| Case report | Italy | 39-year-old male | Left eye blepharoconjunctivitis with a small lesion on the left lower eyelid | Positive in both eyelid and conjunctival swabs | NR | Polymixin B, neomycin and dexamethasone eyedrops | No ocular lesions remained 3 weeks after the onset of the symptoms (redness remained) | [09] |

| Table 1 c | continued | | | | | | | |
|--------------------------|-----------------|--|---|---|--|---|---|------------|
| Type of investigation | Country | Age and sex | Ocular complications | Ocular PCR test for Monkeypox DNA | Systemic treatments | Ocular treatments | Outcome | References |
| Case series | 16 countries | 3 patients with ocular symptoms | Conjunctival lesions | NR | NR | NR | NR | [24] |
| Case series | US | 20–29 year old male | Left eye pain, redness, itching, photosensitivity, discharge, foreign body sensation and vision problem Left eye conjunctivitis with conjunctival lesions and keratitis | Positive in conjunctival swabs | Oral and Intravenous tecovirimat | Topical trifluridine | Over 22 days of hospitalization that was ongoing at the time of the study with considerable vision impairment | [99] |
| Case series | SU | 30–39 year old male | Right eye pain, itching, redness and photosensitivity Right eye conjunctivitis with multiple small conjunctival nodules and corneal ulcer | NR | Oral and intravenous tecovirimat | Topical trifluridine | After 10 days of hospitalization, the patient was discharged with the improvement of eye lesions and no vision changes | [99] |
| Case series | N | 30–39-year- old male | Initially, right eye redness, pain and discharge Extending to bilateral conjunctivitis | NR | Oral tecovirimat | NR | After 1 month of treatment, ocular symptoms were resolved with no vision changes | [99] |
| Case series | ſS | 30-39-year- old male | Right eye pain, redness and periorbital swelling Right eye conjunctivitis, conjunctival and eyelid lesions, and preseptal cellulitis | Positive in both eyelid and conjunctival swabs | Oral tecovirimat and Intravenous antibiotics for preseptal cellulitis | Topical trifluridine and antibacterial drops | After 5 days of hospitalization, the patient was discharged with clinical improvement and no vision impairments | [66] |
| Case series | US | 30–39-year- old female | Left eye pain and redness Left eye conjunctivitis, a lesion on the bulbar conjunctiva and a subconjunctival nodule | NR | Oral tecovirimat | Topical trifluridine | The patient was discharged with no ocular symptoms and vision change 3 days after hospitalization | [66] |
| Case report | SU | 30-year-old male | Ulcers on right lower palpebral conjunctiva, right caruncle and a papule on right upper cyclid | Ocular lesions were not swabbed | Oral recovirimat | Artificial teats and erythromycin | After 6 days of treatment, the patient was discharged from the hospital with improved conjunctival lesions. The eyelid margin became red, and eye irritation resolved without vision impairments | [67] |

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| Table | |

| Type of investigation | Country | Age and sex | Ocular complications | Ocular PCR test for Monkeypox DNA | Systemic treatments | Ocular treatments | Outcome | References |
|--------------------------|-----------|---------------------|---|---|------------------------|--|--|------------|
| Case report | Australia | 38 year-old male | Right eye conjunctival injections, foreign body sensation, epiphora and intermittent blurring of vision Right eye blepharoconjunctivitis with mild edema of lower and upper eyelids, conjunctival hyperemia and medial cantus lesion | Positive in both medial cantus and conjunctival swabs | Oral tecovirimat | Lubricating drops, ointment (paraffin + recinol palmitate) and topical chloramphenicol drops | The patient's symptoms were completely resolved after 1 week of therapy | [68] |

surveillance in the Democratic Republic of Congo (DRC) from 1981 to 1986. The risks of these serious sequels were higher in younger children and in individuals who contracted the virus from animal exposure [28].

The above findings highlight the prominence of risk stratification in susceptible individuals, particularly unvaccinated children, and the necessity of identifying possible MPXV ocular symptoms to prevent them from further progression to permanent sequelae. Due to scarce evidence on ocular disease progression and pattern of symptoms in MPXV infection, it is crucial for further research to shed light on more detailed symptomatology. The ocular manifestations, management and outcomes of MPXV cases within the previous outbreaks are summarized in Table 2.

Animal Studies The study of MPXV ocular symptoms and viral presence in ocular tissues initially came from infected prairie dogs (*Cynomys ludovicianus*) in close contact with African rodents in the 2003 Wisconsin outbreak [7]. Some of these animals were reported to have ocular discharge and necrotizing blepharoconjunctivitis, which was the first symptom of the illness; it made the eyeballs swollen and damaged the cornea and conjunctiva in a multifocal pattern [29, 30].

Furthermore, an animal model for MPXV infection with Gambian Pouched Rats (*Criceto-mys gambianus*) illustrated that after 14 days of virus inoculation through the dermal or nasal route, corneal injuries emerged with unilateral white-yellow opacity and ocular discharge. Additionally, viral shedding from ocular mucosa started 7 days after inoculation and was positive until day 21 post-inoculation [31]. In parallel, the viral DNA detection in ocular swabs was confirmed as early as 9 days post-exposure in a study on a prairie dog (*Cynomys ludovicianus*) model that inoculated animals with two viral clades of West Africa and Congo Basin via similar routes to the former study [32].

| Type of investigation | Country | No. of patients | Ocular complications | Prevalence | Ocular treatments | Outcome | Year (references) |
|--|---------|--------------------|--|--|----------------------|--|----------------------|
| Retrospective chart review | Nigeria | 40 | Conjunctivitis and Photophobia | 22% | NR | NR | 2020 [69] |
| Surveillance data (from 2011 to 2015) | DRC | 1057 | Photophobia Conjunctivitis | 8.5–36.6% 9.7–30.1% | NR | NR | 2021 [70] |
| Retrospective investigation | Sudan | 19 | Conjunctivitis | 60% | NR | NR | 2005 [71] |
| Surveillance data (from 2010–2013) | DRC | NR | Conjunctivitis | 23.1% | NR | Affected cases had a higher frequency of other symptoms and 47% reported being bed-ridden | 2014 [27] |
| Surveillance data in 2003 | US | 34 | Conjunctivitis Frontal headache | 9% 65% | NR | NR | 2005 [17] |
| Review | US | - | Conjunctivitis Corneal ulceration | 30% of the non- immunized vs. 7% of the immunized 4% of the non- immunized vs. 1% of the immunized | NR | Unilateral blindness in 1 patient due to corneal opacification | 2011 [15] |
| Surveillance data (from 1980 to 1985) | DRC | 282 | Lesions on eyelids and conjunctiva | 17% of unvaccinated 13% of vaccinated individuals | NR | Corneal ulceration in 4% of unvaccinated individuals. Bilateral and unilateral blindness occurred in 1 and 4 patients, respectively | 1987 [14] |

Table 2 Ocular manifestations, management and outcomes of monkeypox during previous outbreaks

| Type of investigation | Country | No. of patients | Ocular complications | Prevalence | Ocular treatments | Outcome | Year (references) |
|--|---------|--------------------|-------------------------|---|----------------------|---|----------------------|
| Surveillance data (from 1981 to 1986) | DRC | 338 | Conjunctivitis | 20.3% of the unvaccinated with an animal source infection | NR | Visual loss in 10% of primary and 5% of secondary cases | 1988 [28] |
| | | | | 16.4% of the unvaccinated with a human source | | | |

 Table 2 continued

DIFFERENTIAL DIAGNOSIS OF MONKEYPOX

Despite MPXV ocular damage, other orthopoxviruses and their vaccination contribute to similar corneal infections and complications. One of the most rigorously investigated poxviruses is smallpox. Lymphadenopathy, present primarily in the early stages of the MPXV infection, is the core factor differentiating MPXV, smallpox and chickenpox infection [14]. Ocular manifestations have been reported in 5–9% of smallpox cases, and from its shared features with MPXV, corneal ulceration is the most frequent sequel that further threatens the vision by several routes such as perforation and endophthalmitis [33].

Ocular vaccinia should be suspected in a patient with pustular lesions on the eyelid or conjunctiva with a recent immunization history or recent contact with a smallpox vaccine recipient [34, 35]. Blepharoconjunctivitis is caused by accidental eye rubbing after touching the active smallpox immunization site by the vaccinee (autoinoculation) or close contact [34, 36]. The incidence of ocular vaccinia following smallpox vaccination is about 10 to 20 cases per 1 million primary immunizations, and it is associated with more complications compared with revaccinated cases [33]. While the risk of this event was estimated to be the same

between the two traditional smallpox vaccines, Dryvax, also known as ACAM2000 [37], the newly approved non-replicating vaccine for smallpox, and MPXV, MVA-BN (Modified Vaccinia Ankara-Bavarian Nordic) vaccine, do not lead to the development of ocular vaccinia.

Herpes simplex virus (HSV), varicella zoster virus (VZV), and Molluscum contagiosum (MC) infections can also mimic the ocular presentations of orthopoxviruses. The primary ocular HSV-1 infection is mainly asymptomatic, while it can still resemble MPXV ocular manifestations by presenting with blepharoconjunctivitis and superficial punctate keratitis (SPKs) [38]. Moreover, the recurrent HSV ocular characteristics fall into three major categories; keratitis, uveitis and retinitis. Herpes zoster ophthalmicus is caused by the reactivation of latent VZV, and diagnosis should be focused on a history of previous rash or skin findings [39]. It can mimic ocular forms of poxviruses by causing conjunctivitis, epithelial keratitis and anterior corneal infiltrates [40, 41]. MC, caused by a virus from the poxvirus family, is characterized by skin or mucosal papular eruptions (usually 2-6 mm) with a white pearly caseous substance in the center [42] that can occasionally afflict the eyes. They most commonly appear on eyelids and can progress further to cause follicular conjunctivitis, keratitis and rarely pannus [43, 44].

MANAGEMENT OF OCULAR COMPLICATIONS

Decades before smallpox eradication, eye-protective measures were limited to the application of ophthalmic lubricants and intake of systemic vitamin supplementation to prevent secondary bacterial infections with potential catastrophic complications, including corneal ulceration, perforation, anterior staphyloma and phthisis bulbi [45]. Later on and amid the smallpox mass vaccination, topical antivirals, including idoxuridine, trifluridine and vidarabine, were used to treat or prevent cornea or conjunctiva involvement as in ocular vaccinia or ocular smallpox [33].

On the other hand, trifluorothymidine (trifluridine). an anti-herpesvirus fluorinated pyrimidine nucleoside that inhibits viral DNA synthesis, has been used more frequently. Although its efficacy has not been supported by any clinical trial yet, some evidence from case reports and animal studies supports its use in ocular vaccinia keratitis and conjunctivitis [46]. Among several cases with inadvertent ocular inoculation of orthopoxviruses [34, 47], trifluridine has shown a favorable effect in alleviating the symptoms and preventing permanent scarring. However, some case reports found it ineffective for treating acute ocular complications of cowpox and another orthopox virus [48, 49]. WHO recommends it for the management of monkeypox ocular complications [50]. Prophylactic use may hinder the deterioration of palpebral and peri-ocular to conjunctival and/or corneal lesions [51].

Oral or systemic antibiotics may be considered for treatment or prophylaxis in ocular MPXV as was indicated for prophylaxis against ocular vaccinia bacterial superinfection in the presence of keratitis [34].

Topical steroids may prevent monkeypox keratitis or iritis [50]. However, concurrent use of steroids with topical antivirals should be considered. Otherwise, the viral clearance from the eye may take longer [52]. Topical steroids may be considered for reducing inflammation in severe keratitis only when the corneal epithelium is intact and the active infection is resolved, in conjunction with antiviral therapies. Besides, vaccinia immune globulin (VIG) may be considered for administration in severe ocular complications. Still, its use should be limited or weighed carefully in the presence of keratitis to avoid potential corneal scarring, probably through the aggregation of antigenantibody complexes [33, 34].

Clinicians should abstain from administering aciclovir and ganciclovir for monkeypox treatment as they are effective herpesviruses and not orthopoxviruses [53]. Despite a lack of clinical trials on the safety and efficacy of Monkeypox antivirals, they shall be used under expanded access protocols, including Monitored Emergency Use of Unregistered and Investigational Interventions [50].

Oral tecovirimat (600 mg two times per day for 2 weeks), an inhibitor of the viral envelope protein VP37, is the most prominent of these antivirals. It is recommended for severe forms of the disease, such as patients with ocular or periorbital manifestations [54]. Tecovirimat is approved by the European Medicines Agency for the treatment of monkeypox and in the USA, Canada and Europe for human smallpox disease. Nonetheless, it is still not FDA-approved for monkeypox treatment [54]. Administration of tecovirimat for 5-7 days in monkeypox animal models has shown promising clinical and virological outcomes, yet the duration of treatment is still higher in humans due to suspicion of an early rebound following a premature cessation of the treatment [53].

In vitro and animal investigations have shown cidofovir and its prodrug to be also effective against orthopoxviruses [50]. Prolonged use of cidofovir in HIV-related cytomegalovirus (CMV) retinitis can help the development of anterior uveitis with hypotony. It does not necessarily indicate the termination of treatment [55].

Apart from antivirals and antibiotics, steroids and vitamins may also be effective. Vitamin A supplement could be considered for the malnourished as it helps the wound-healing process [50].

DISCUSSION

Monkeypox has been a widely neglected virus for a very long time. The very recent outbreak of the virus in non-endemic areas has raised considerable concern regarding the disease's shortand long-term complications. There is a vast knowledge gap regarding monkeypox ocular symptoms, long-term complications and therapeutics. Much of the data on the MPXV ocular signs and symptoms come from sporadic case reports, and further studies should be directed at outstanding clinical trials and original investigations. The ocular complications of the MPXV cases during the 2022 outbreak are representative of a potential shift in frequency and pattern. Although it is yet too premature to confirm this statement, the recent cases were indicative of less frequent [56] and more subtle and self-limited symptoms [56-60] than in previous outbreaks in endemic countries [14, 15, 18, 28, 61] and rarely resulted in permanent sequelae.

Based on the present data, MPXV can manifest as eye redness, photophobia, frontal headache, orbital and peri-ocular vesicular and pustular rashes, blepharitis, lacrimation, ocular discharge, conjunctivitis, subconjunctival nodules, keratitis and subsequent corneal ulceration, opacification, perforation and blindness. These complications may occur more frequently and devastatingly in those without prior immunization against smallpox.

Occasionally, the corneal, conjunctival and eyelid involvement in monkeypox infection is a bacterial rather than a directly toxic viral phenomenon and thus may respond quickly to antibiotics [11]. A negative monkeypox DNA polymerase chain reaction (PCR) from the ocular samples may raise suspicion of a bacterial infection [11].

It is still unclear whether the ocular involvement is a result of the systemic spread of the virus in the early viremic phase of infection or is secondary to self-inoculation. Interestingly, it has been demonstrated that smallpox, a similar virus from the pox family, can be actively secreted into tears and thus play a role in the spread of the disease [62]. Hence, it is

Ophthalmol Ther (2023) 12:55-69

a path of disease propagation, particularly when preceding cutaneous lesions [63]. Comparing the positive results of monkeypox DNA PCR from ocular and cutaneous swabs, the more prolonged clearance of the virus from the ocular than cutaneous lesions may contribute to longer disease transmissibility [56]. Despite some hypotheses regarding the passage of MPXV into the conjunctival secretions via the plasma compartment, the emergence of cutaneous lesions before ocular involvement may suggest self-inoculation as the culprit [56]. A case described by Meduri et al. also raised this hypothesis as two separate PCR tests from ocular and cutaneous samples had close cycle threshold values, suggesting a transmission via eye contact [64]. Accordingly, healthcare professionals should be extra vigilant and recruit appropriate preventive measures.

Regarding treatment, monkeypox is mostly a mild to moderate self-limited entity. Hence, there is no need for the proactive use of antivirals for disease containment [24]. Nonetheless, in severe cases or when the lesions are located at sensitive sites like ocular involvement, administration of specific antivirals may be indicated [65]. For MPXV ocular complications, simple therapies like regular lubrication and prophylactic use of topical antibiotics should be considered [45].

Severe sequelae and sight-threatening complications tend to occur more in unvaccinated individuals (74%) than in vaccinated populations (39.5%) [20]. Thus, encouraging people to take vaccines by promoting public awareness is of paramount importance.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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