Monkey Pox – A Review

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Abstract

The current epidemic of monkey pox is the largest in history to occur outside of Africa. Monkey pox is an budding zoonotic disease that for decades has been viewed as an infectious disease with outbreak potential as its occurrence is increasing in recent years. As public health entities work to contain the current outbreak, healthcare professionals globally are aiming to become familiar with the various clinical presentations and management of this infection. We present in this review an updated overview of monkeypox for healthcare professionals in the context of the ongoing outbreaks around the world.

Keywords: Emerging Infectious Diseases, Monkeypox, Outbreak.

Introduction

In the year 2022 outbreak of monkeypox involving multiple countries in both endemic and nonendemic regions has generated significant international interest [1, 2]. A once-neglected zoonotic virus endemic to West and Central Africa, monkeypox virus was first identified in 1958 [3] in nonhuman primates kept for research in Denmark [3]. The first case in humans was reported in 1970 in the Democratic Republic of Congo [4]. Over the past 50 years, sporadic outbreaks have been reported mainly in African countries, with several thousand human cases recorded to date. Occasional cases and limited outbreaks linked to travel or importation of animals harboring the virus have also been described in nonendemic countries [5]. It has long been a theoretical concern that monkeypox virus and other zoonotic poxviruses could over time expand to fill the ecological niche once occupied by the closely related variola virus [6, 7]. The combined effects of deforestation, population growth, encroachment on animal reservoir habitats, increasing human movement, and enhanced global interconnectedness have made this possibility more real in the last 20 years [6–8].

With increasing case numbers being reported in the current outbreak, it is important for clinicians everywhere to update their knowledge of this zoonotic infection, including its prevention, clinical management, prophylaxis, and basics of infection control, to understand the broader implications of the current outbreak. In this review, we provide an overview of monkeypox virus infection to serve as a primer for healthcare professionals who may encounter this condition in their practice.

History

Recognition of Monkeypox in Nonhuman Primates Smallpox has been a disease of major importance to man for many centuries . Naturally occurring epidemics of pox diseases among nonhuman primates have occasionally been reported. In their survey in 1968, Arita and Henderson found seven recorded episodes of pox diseases in nonhuman primates; one of these was confirmed by virus isolation [6]. In 1958, von Magnus et al. (7) observed two outbreaks of a nonfatal poxlike disease in two shipments of cynomolgus (Macaca cynomolgus) monkeys arriving in Copenhagen after shipment from Singapore. A poxlike skin eruption developed among the animals between 51 and 62 days after arrival in Copenhagen.

Approximately 20 to 30% of the animals developed clinical illness. The epizootics in

Copenhagen suggested slow recruitment of susceptible monkeys in a cycle of inapparent infections with subsequent intensification and the emergent clinical expression of monkeypox. Whether the risk of disease was dependent upon intensified replication of MPV in vivo or enhanced invasiveness, or both, is unknown.

We assume that the primary source of MPV came from a companion monkey; whether MPV came from a recent (nasopharyngeal colonization) or remote (latent carrier of virus in tissues) infection is also unknown. The latter kind of origin is possible since a virus analogous to MPV has been recovered from the kidneys of apparently healthy monkeys (quoted in 5, 6.Viruses isolated from the dermal lesions of affected monkeys produced pock lesions on the chorioallantoic membrane (CAM) of developing chicken embryos, cytopathic effects (CPE) in mammalian cell cultures, encephalitis in mice, and dermal lesions, as well as keratitis, in rabbits.

In 1959, an outbreak of monkeypox occurred in the animal quarters of Merck, Sharp, and

Dohme in Philadelphia . Within a colony of 2,000 monkeys (56% Macaca mulatta, 41% Macaca philippinensis, and 3% Cercopithecus aethiops var. subaeus) at least 10% of companion monkeys were considered to have been infected. Less than 0.5% of those affected died. The affected monkeys were predominantly Macaca philippinensis, although Ma- caca mulatta also developed clinical evidence of disease.

During 1962, monkeypox was recognized in the primate colony of the Walter Reed Army Institute of Research, Washington, D.C. The disease was observed initially in a cynomolgus monkey which had been given total body irradiation. Subsequently, similar lesions developed in two other cynomolgus monkeys; of the two, one had been irradiated; the other, an apparently healthy animal, was untreated.Both irradiated monkeys died of the disease, whereas the healthy animal survived. Monkeys in the colony were studied serologically in order to determine rates of past infection. Among 27 cynomolgus monkeys exposed to MPV, 25 (93%) had specific antibodies, whereas, in another group of 45 cynomolgi wherein exposure had been unrecognized, only 5 (11%) had specific antibody. Fifty-two of 67 rhesus, and 6 of 14 African green monkeys were also seropositive.

In 1964, Peters reported an outbreak of monkeypox in the Zoological Garden, Rotterdam, Netherlands. The affected animals included giant anteaters (Myrmecophaga tridactyla), orangutans (Pongo pygmaeus), chimpanzees (Pan troglodytes), gorillas (Gorilla gorilla), guenons (Cercopithecus sp.), squirrel monkeys (Siamiri sciurea), macaques (Macaca sp.), gibbons (Hylobates lar), and marmosets (Hapale jacchus) .

Eleven of the 23 affected animals died, including 6 of 9 orangutans, 3 squirrel monkeys, 1 gibbon, and 1 marmoset. MPV was isolated from 1 of the anteaters, 7 orangutans, and 3 monkeys of various species (31). During 1964 and 1965, three silent MPV infections were recognized in colonies of cynomolgus monkeys at Utrecht, Netherlands. These infections were recognized by recovery and identification of a virus obtained from kidney cells cultured from apparently healthy monkeys [7,8].

In 1967, the World Health Organization (WHO) surveyed 26 major biological institutes

in which large numbers of monkeys were used to study outbreaks of monkeypox. Besides thefive outbreaks confirmed by virus isolation mentioned above, there were in the U.S.A., between 1965 and 1967, four other instances of poxlike disease compatible with monkeypox; none of the diseases was confirmed virologically[6].Marennikova et al. subsequently compared the properties of five strains of MPV,four of the five MPV strains tested were similar in biological properties and could be readily distinguished from both variola and vaccinia viruses. A fifth strain differed from the other four in several characteristics and had properties indistinguishable from variola virus.

Virology

The *Poxviridae* family are double-stranded deoxyribonucleic acid viruses which infect a range of animals including birds, reptiles, insects and mammals. The family consists of 2 subfamilies: *Chordopoxvirinae* (with 18 genera and 52 species) and *Entomopoxvarinae* (with 4 genera and 30 species). Monkeypox belongs to the *Poxviridae* family, the *Chordopoxvirinae* subfamily, and the genus *Orthopoxvirus* [9–11]. Several poxvirus species have been shown to cause human infections including *Variola* (smallpox), *Cowpox*, *Monkeypox*, *Vaccinia*, *Camelpox*, *Alaskapox*, *Yaba monkey tumor virusTanapox virus*, *Orf virus*, *Pseudocowpox virus*, *Bovine papular stomatitis virus, Buffalopox* and *Molluscum contagiosum.* Humans are the reservoir host of Variola and Molluscum contagiosum viruses [11]. Monkeypox virus (MPXV) has a wide range of potential host organisms, which has allowed it to circulate in wild animals for a prolonged period of time while sporadically causing human disease through spillover events [9]. More importantly, Orthopoxviruses (OPXV) exhibit immunological cross-reactivity and cross-protection, and infection with any member of the genus confers some protection from infection with any other members of the same genus [12, 13].

Orthopoxviruses are large (size range:140–450 nm) viruses with a brick-like structure and a genome consisting of approximately 200-500kbp kb [6, 9, 10] that codes for over 200 genes. Many of the genes encoded by the OPXV genome are not essential for virus replication in cell culture but might play important roles in the host antiviral response [10, 14].

All poxviruses complete their replication cycle in the cytoplasm of infected cells via complex molecular pathways [10, 15]. This intracellular replication cycle has been well characterized for Vaccinia virus, which was used to develop the vaccine that helped to eradicate smallpox globally; key features of this replication cycle are similar for all poxviruses [10, 15]. The infection cycle

can be initiated by two distinct forms of the virus: the intracellular mature virion and the extracellular enveloped virion, which differ in their expression of surface glycoproteins. Glycosaminoglycans, which are ubiquitously expressed on the surface of mammalian cells, are thought to be crucial for binding of the virion to the cell membrane, although all cellular receptors have not been fully characterized [10, 15]. A detailed description of the replication cycle is beyond the scope of this review but has been described previously [10, 15].

Smallpox is estimated to have caused millions of fatalities worldwide [13] and was one of the most dreaded infectious diseases in human history. The impact of smallpox serves as a reminder that OPXV can be formidable pathogens. Although the origins of smallpox are not known, there is some evidence which suggests that Variola virus may have evolved from an ancient rodent poxvirus thousands of years ago [16]. The increasing danger of zoonotic *OPXV* infections such as *MPXV* has been recognized for a long time [17, 18]. As a consequence of immunization programs against smallpox ending over 40 years ago, a significant proportion of the global population does not have immunity against smallpox and zoonotic *OPXV*. All of this raises the possibility that given the right conditions, such as increasing incidence of human infections and long-term absence of vaccine immunity, a zoonotic orthopoxvirus like *MPXV* could acquire the ability to more efficiently transmit between humans and cause larger outbreaks [17].

Routes of Transmission

Monkeypox has developed in monkeys following intradermal, subcutaneous, intramuscular, and intravenous inoculation of MPV . Clinical and subclinical infections regularly develop among uninoculated companion monkeys separately caged among experimentally infected animals. The natural route of these latter infections is presumably by the respiratory pathway, although autoinoculation or ingestion of viral particles, or both, are possible portals of entry.

Clinical Presentation

In the context of exposure and in the sylvatic setting persons are at increased risk for developing monkeypox if they live in forested areas and are male gender, are less than 15 years of age, and are not immune to smallpox [18]. Historically, patients have typically presented with prodromal symptoms, including fever, headaches, chills, malaise, and lymphadenopathy, followed by development of a characteristic rash.

The rash usually starts in the mouth, and then spreads to the face and extremities, including the palms and soles. Each lesion begins as a macule and then progresses to papules, vesicles, pustules, and scabs. Pain can be prominent, but it is not universally present, and pruritus can occur when the lesions are in the healing stage. Unlike chickenpox, skin lesions due to monkeypox tend to be similar in size and typically present at the same stage. The number of lesions can range from 10 to 150 and can persist for up to 4 weeks [18]. Patients are infectious from the time symptoms start (presumed to include prodromal symptoms before the appearance of the rash) until the lesions scab and fall off, with a new layer of skin being formed [8]. In rare instances, patients can experience complications of monkeypox, such as bacterial superinfection, encephalitis, pneumonitis, and conjunctivitis/keratitis [17]. The timeframe for developing complications and their rates have not been systematically determined [19].

Many features of monkeypox are similar to smallpox [74]; however, in contrast to smallpox, monkeypox is often milder and presents with lymphadenopathy, which was typically absent in smallpox infection. It is also

important to note that the cutaneous manifestations of monkeypox can be confused with other infections, including chickenpox, molluscum contagiosum, herpes simplex virus, syphilis, impetigo, measles in the early stages, and rickettsial diseases.

In the current 2022 outbreak, the presentation of monkeypox has had atypical features in many patients. For example, the characteristic rash is still present, but it can be limited to the genital, perigenital, and perianal areas and present at different stages of development [20,21]. In addition, patients may present with only mild or absent prodromal symptoms which may begin after onset of a localised rash [21]. Therefore, it is crucially important to consider a wide spectrum of disease presentations as clinicians aim to accurately diagnose patients while the world attempts to contain the outbreak.

Diagnosis

It is important to have a high index of suspicion for monkeypox infection and to be aware of the sometimes atypical presentations of the infection that have been described in the ongoing 2022 outbreak. When there is clinical suspicion for monkeypox, clinicians should ask about travel and sexual history and about any close contacts with people with a similar rash or suspected or confirmed monkeypox infection. Behaviors associated with close contact include sleeping in the same room, drinking or eating from the same container, living in the same residence, etc [7]. More importantly, absence of travel history or absence of a specific known close contact with a rash or with suspected or confirmed monkeypox infection should not exclude the possibility of this diagnosis. A thorough skin examination should also be performed.

The optimal diagnostic procedure for a patient with suspected active monkeypox infection is to obtain a specimen from a skin lesion to send for molecular testing by PCR. Ideally, more than 1 specimen should be obtained from 2 separate lesions on different parts of the body, and lesions should be unroofed to adequately sample virus containing secretions.

Certain laboratories can perform direct PCR testing for *MPXV* specifically, whereas others perform generic *OPXV* testing that requires confirmatory testing for *MPXV* at a reference laboratory. However, in the context of the current outbreak, a positive *OPXV* test can reasonably be concluded to represent a diagnosis of monkeypox infection before results from confirmatory testing are available. Testing plans should ideally be coordinated with public health authorities in advance of specimen collection.

Cell culture provides virus strains for further characterization, but it is restricted to accredited biosafety level 3 reference laboratories [22]. Serological testing can potentially be helpful in epidemiologic investigations, retrospective diagnosis of past infections, and diagnosis of late clinical manifestations, such as encephalitis. *MPXV* serology can cross-react with prior smallpox vaccination, but this is not a concern in unvaccinated individuals [23].

Treatment

The mainstay of clinical management for typical monkeypox infection is supportive care . Supportive care [20] includes maintenance of adequate fluid balance (because of the possibility of increased insensible fluid losses from the skin, decreased oral intake, and vomiting or diarrhea). Other measures such as hemodynamic support, supplemental oxygen, or other respiratory support and treatment of bacterial superinfections of skin lesions should be considered where indicated. Another aspect of supportive care that has been described with previous *OPXV* infections is management of ocular infection/complications, specifically resulting in corneal

scarring and/or loss of vision [24]. Potential approaches to consider in this situation include early involvement of ophthalmology experts, application of lubricants, topical antibiotics, and possibly topical antivirals such as trifluridine [24].

At the present time, there are no US Food and Drug Administration (FDA)-approved treatments specifically for monkeypox. However, there are antiviral agents that have activity against *MPXV* , including cidofovir, brincidofovir (a lipid-conjugate prodrug of cidofovir), and tecovirimat . In addition to antiviral agents, vaccinia immune globulin intravenous (VIGIV) has been previously approved by the FDA for treatment of complications due to vaccinia vaccination, such as progressive vaccinia and severe generalized vaccinia [25,26,27]..

Currently, tecovirimat, cidofovir, and VIGIV are available from the Strategic National Stockpile under Expanded Access Investigational New Drug (EA-IND) protocols held by the Centers for Disease Control and Prevention (CDC) for treatment of *OPXV* infections in an outbreak scenario [28]. In the United States, these medications can be accessed through the CDC via requests from state and territorial health departments.

Cidofovir

Cidofovir was approved by the FDA in 1996 for the treatment of patients with retinitis caused by cytomegalovirus (CMV) in patients with the acquired immunodeficiency syndrome. Cidofovir has broad antiviral activity against viruses from different families, including herpes viruses, adenovirus,an OPXV. With regards to its use in *OPXV* infections, cidofovir was used as part of the treatment regimen for a 28-month-old boy with refractory atopic dermatitis who developed severe eczema vaccinatum after being in contact with his father,

who had received smallpox vaccination . The child survived without long-term sequelae [29].

Brincidofovir

Brincidofovir was approved by the FDA for the treatment of smallpox infection in June 2021 . It has previously been used in patients with CMV infection [104], adenovirus [105], and OPXV infections. Brincidofovir was used as part of a combination therapy regimen for a patient who received smallpox vaccination and was diagnosed with acute myeloid leukemia (AML) shortly thereafter . After induction chemotherapy, the patient developed progressive *Vaccinia* and was treated with multiple drugs, including 6 doses of brincidofovir. This agent was also used in the treatment of a 17-year-old kidney-transplant recipient with ultimately fatal disseminated cowpox virus infection . In May 2022, Adler et al [89] described clinical management of 7 patients with *MPXV* infection in the UK. In this case series, 3 patients received brincidofovir and all of 3 patients developed elevated liver enzymes, a well described side effect associated with brincidofovir use, which led to cessation of treatment [30,31].

Tecovirimat

Tecovirimat was approved by the FDA in 2018 for the treatment of smallpox infection [32]. It was also approved by the European Medicines Agency in January 2022 for treatment of smallpox and cowpox [107]. It has been used in several case reports for the treatment of disseminated and ocular infections with cowpox [32] and *Vaccinia* infection as part of a multidrug treatment regimen [33]. Tecovirimat was also used as prophylaxis to prevent development of progressive *Vaccinia* in a 19-year-old man who had received smallpox vaccination and was diagnosed with AML soon after vaccination [30]. In this case, tecovirimat was used continuously for 61 days specifically as prophylaxis while the patient was

receiving chemotherapy for leukemia. The patient developed skin lesions due to inadvertent autoinoculation after vaccination, without progression or dissemination. Tecovirimat has also been used in a patient with keratoconjunctivitis due to cowpox, although a detailed clinical description of this case is not available [34]. Tecovirimat was also used in a laboratory worker who had a needlestick exposure to *Vaccinia* virus [34]. Other instances in which tecovirimat has previously been used are outlined in Table 3. With regards to *MPXV* infections specifically, tecovirimat was used to treat a patient with a travel-associated case of monkeypox in the United States in 2021 [19]. In July 2021, an expanded access protocol was announced for the Central African Republic, with a plan for 500 courses of tecovirimat

to be used for treatment of monkeypox [35]. In the recent case series by Adler et al [8,9], 1 of 7 patients received tecovirimat for 2 weeks. The patient experienced no adverse effects and had a shorter duration of viral shedding and illness [31]. Finally, in the CDC's report on the initial 17 patients with confirmed *MPXV* infection in the United States during the ongoing 2022 outbreak, 1 patient received tecovirimat [35].

Vaccinia Immune Globulin Intravenous

Vaccinia immune globulin intravenous was approved by the FDA in 2005 for treatment of complications due to vaccination with the *Vaccinia* virus [36]. Before this, Vaccinia immune globulin was administered as an intramuscular (IM) injection. The historical use of IM Vaccinia immune globulin has been extensively reviewed and summarized [110]. The FDA approval of the intravenous formulation of vaccinia immunoglobulin (VIGIV) has been used in several published reports for human *OPXV* infections. Many of the patients described in the case reports outlined in Table 3 also received VIGIV in combination with antivirals for treatment of

their *OPXV* infections [31-35]. Vaccinia immune globulin administered intravenously was additionally used in a patient with inflammatory bowel disease who developed infection after eexposureee to a vaccinia-rabies glycoprotein recombinant virus used in animal bait to help control the spread of rabies in the animal population. It was also used to treat two patients who developed symptomatic Vaccinia infection through secondary and tertiary transmission after initial sexual contact between a smallpox vaccine recipient and one of the case-patients [36].

Overall, the natural history of MPXV infection in humans is mild to moderate disease with a self-limited course for many patients. Antiviral therapy should be considered for the following; severe illness requiring hospitalization; ocular, oral, and/or perineal involvement; and in patients considered at higher risk for progression to severe disease (immunocompromised, children <8 years of age, pregnant or breastfeeding persons, and the presence of atopic dermatitis or other active exfoliative skin conditions) [32]. The most practical clinical experience is with tecovirimat, which is the preferred antiviral drug. Treatment for MPXV infection should ideally be given in the context of a clinical trial where feasible, to generate long-term evidence that could inform on how best to treat patients in the future. Clinicians are encouraged to coordinate treatment plans and approaches with infectious disease experts and public health authorities.

Immunization

Infection with OPXV can confer immunological cross-protection between viruses of the same genus [9, 12, 13]. There are no vaccines specifically designed to protect against monkeypox infection and disease. The vaccines being considered for use (Vaccinia virus-based vaccines) to prevent MPXV were developed for smallpox. In a

study conducted in the DRC in the late 1980s [37], the unvaccinated household contacts of individuals with MPXV disease had a secondary attack rate of 9.28% compared to 1.31% for vaccinated contacts. This yielded a rough estimate of 85% protection conferred by prior smallpox vaccination against monkeypox [15, 31]. Before 2019, ACAM2000 was the only OPXV vaccine available in the United States. ACAM2000 is made from a live, replication-competent Vaccinia virus, a member of the OPXV genus. Due to its replication competent property, there is a risk for serious adverse events associated with use of ACAM2000 (eg, progressive vaccinia [38], eczema vaccinatum [39], and myopericarditis [40,41].Vaccinia can also be transmitted from a vaccinated person to unvaccinated individuals through close contact with the vaccination site. By contrast, Jynneos (also known as Imvamune and Imvanex) is a nonreplicating modified Vaccinia Ankara virus vaccine. It was licensed for both prevention of monkeypox and smallpox in the United States in 2019. Unlike ACAM2000, Jynneos does not lead to the production of live virus in vaccinated individuals and, as such, is considered safer for use in immunocompromised individuals. It is important to note, however, that the immune response to Jynneos vaccine can be diminished in immunocompromised patients; therefore, protection might not be as robust as in immunocompetent individuals [42]. Both vaccines are authorized for use in individuals older than 18 years. There are limited data on the efficacy of Jynneos in preventing MPXV in humans. Its efficacy is inferred from vaccine efficacy studies using animal models (prairie dogs and cynomolgus macaques) [43] and safety and immunogenicity studies in humans [41]. A third vaccine, Aventis Pasteur Small Pox Vaccine, is an experimental smallpox vaccine made from replication-competent Vaccinia virus, similar to ACAM2000. It may be used in the United States under Investigational New Drug protocol or via emergency use authorization in circumstances where the other 2 vaccines are not available. ACAM2000 and Jynneos have been studied as postexposure prophylaxis (PEP) using intranasal challenge animal models [44]. Both vaccines conferred some degree of protection against monkeypox at lower inoculum doses. Administration of vaccine at 1 day postexposure was more effective than administration at 3 days postexposure for Jynneos, but ACAM2000 was similarly effective at either postexposure vaccination timepoint [45]. Vaccination of healthcare workers against monkeypox in the DRC was safely conducted as part of real-world feasiibility and immunogenicity studies with ongoing follow-up [46].

Conclusions

MPV was isolated in 1958 during outbreaks of a pox disease in laboratory colonies of cynomolgus monkeys in Copenhagen. Since then, several outbreaks have occurred in different species of non-human primates housed in laboratories in various parts of the world. Naturally occurring infections among monkeys in their native habitat is unknown; however, the appearance of infection by MPV in children residing in West Africa suggests that wild monkeys (or related species) are the likely harborers of MPV.

Studies on the biological properties of MPV indicate that it is closely related to the vaccinia- variola subgroup of poxviruses. MPV produces pock lesions on the CAM of developing chicken embryos, encephalitis in mice, and characteristic dermal lesions and keratitis in rabbits. Morphologically, the virus is 200 by 250 nm in size and has a rectangular shape. Many mammalian cells in culture support the growth of MPV. Cytopathic effects and plaque formation can be easily produced in cultured

cells.Clinically, monkeypox as found in monkeys and in human beings cannot be differentiated from variola.

Serological surveys to determine the frequency of specific antibody to poxviruses in different monkey populations show wide ranges between species; on the average, less than 12% of monkeys originating from different parts of the world contain HI antibody. Whether acquisition of infection was in their native habitat, or followed captivity, remains unknown.

Epidemiological surveillances suggest that a natural reservoir of smallpox in nonhuman primates is unlikely; however, further observations are needed, particularly with respect to monkey populations with high infection rates based on existent HI antibodies.

MPV is pathogenic to man; this feature undoubtedly has clinical and epidemiological significance. Protection of human beings against monkeypox by vaccination with vaccinia virus is mandatory among those who handle monkeys or tissue cultures of primate species.

Uniquivocal answers cannot be given to questions asked in the introductory section. If monkeypox is variola, the contagiousness is exceptional, for variola virus is not easily acquired by sentinel companions quartered among infected monkeys. If infection relates to vaccinia virus, it is unique also, for to our knowledge generalized vaccinia has never been reported in healthy primates (immunologically and dermatologically intact). If it is a hybridvirus of recent or remote origin derived by reactivation in vivo of variola and another poxvirus, it is yet to be described. Finally, if it is uniquely a primary poxvirus (MPV) of monkeys, as it well might be, many of its principal properties have been defined.

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