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Resurgence of Monkeypox Virus Disease in Humans: A Review

Raut A[1]* and Kasarla RR[2]

[1]Medical Officer, Himal Hospital, Nepal

[2]Professor & Head, Department of Microbiology, Universal College of Medical Sciences, Nepal

***Corresponding author:** Anisha Raut, Medical Officer, Himal Hospital, Kathmandu, Nepal, Email: anisha1040@gmail.com

Review Article

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Abstract

A once neglected zoonotic monkeypox virus endemic to West and Central Africa generated significant international interest, due to its emergence causing an outbreak in 2022 involving multiple countries in non-endemic regions. A total of 780 confirmed cases were reported worldwide (across 27 non-endemic countries) as of June 2, 2022, since 13 May 2022. Thus, human monkeypox is an emerging viral zoonotic disease recognized as the most important Orthopoxvirus infection in the smallpox post-eradication era. The waning herd immunity associated with discontinuation of smallpox vaccination may be responsible for resurgence of monkeypox. It is usually a self-limited disease, and the clinical presentation resembles that of smallpox, resulting in a rash similar to smallpox although clinically less severe. Monkeypox is transmitted to humans through close contact with an infected person or animal, or with material contaminated with the virus. Monkeypox virus is transmitted from one person to another by close contact with lesions, body fluids, respiratory droplets, and contaminated materials such as bedding, towels, and clothing. Antiviral drug developed for the treatment of smallpox has also been licensed for the treatment of monkeypox. The knowledge and scientific information on monkeypox virus disease is still unknown or relatively limited to many clinicians, and received little attention. In this review, we provide an overview of monkeypox virus infection to highlight its importance and further research.

Keywords: Monkeypox; Outbreaks; Rash; Zoonotic

Introduction

For well over a decade, members of the scientific community have been concerned about the potential of a monkeypox epidemic. Monkeypox is a rare viral zoonotic disease that occurs primarily in tropical rainforest areas of central and West Africa resulting in a rash similar to smallpox although clinically less severe [1]. With the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination and consequent drop of immunity against orthopoxviruses, monkeypox emerged as the most important virus for public health [2,3]. Cases of Monkeypox that have been detected in countries outside of Africa (Europe, North America) were linked to international travel or imported animals. The sudden and unexpected emergence of the virus in separate populations around the world, in non-endemic countries alarmed scientists. On July 23, 2022 the WHO declared the escalating global monkeypox outbreak a Public Health Emergency of International Concern (PHEIC) [4].

Virology

Poxviruses are large (200-250 nm), enveloped dsDNA viruses with a brick-like structure. The species monkeypox

virus belongs to the Poxviridae family, the Chordopoxvirnae sub-family and the genus *Orthopoxvirus* [5]. Eleven poxvirus species have been shown to cause human infections to date including Variola (smallpox), Cowpox, Vaccinia, Molluscum contagiosum, Orf virus, Camelpox, Yaba monkey tumor virus, Tanapox virus, Pseudocowpox virus, Bovine popular stomatitis virus, and monkeypox. Humans are the exclusive hosts of Variola and Molluscum contagiosum viruses. Unlike Variola, monkeypox virus circulated in a wide range of wild animals for a prolonged period of time, sporadically causing human infection [6].

The monkeypox virus constitutes of two different strains in different geographic regions of Africa: Clade 1 (central African) has been responsible for disease in the Congo Basin and is the more virulent (up to 10% mortality) and the less virulent West African clade 2 (up to 1% mortality). Cameroon is the only country where both virus clades exist. However, there may be a third strain related to clade 2 that have been identified in the 2022 European/North American outbreak [7,8]. Cumulatively, more cases of the central African clade have been reported to date than cases due to the West African clade due to the high number of cases recorded in historical and ongoing outbreaks in the Democratic Republic of Congo. The West African clade has been isolated from cases in non-endemic countries in the May 2022 multi-country outbreaks (Figure 1).

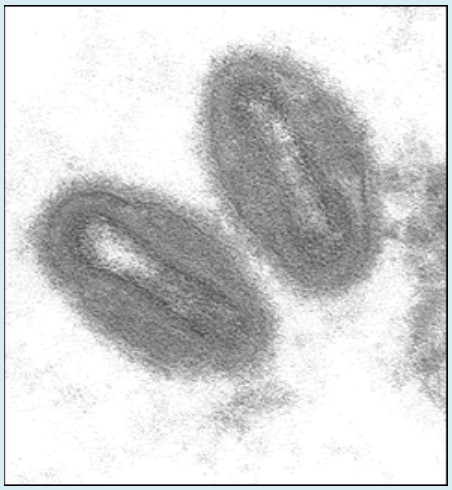

Figure 1: Electron micrograph showing monkeypox virus [9].

Natural Host

Although this virus gets the name from being isolated in monkeys kept for research, monkeys are not the primary reservoirs of the virus. Squirrels, rats, mice, monkeys, prairie dogs, and humans are susceptible to monkeypox virus [10]. The natural reservoir of monkeypox virus has not yet been identified. Available data suggests African rodents as the reservoirs [11].

Epidemiology

Monkeypox was named so after two outbreaks of a pox-like disease in monkeys kept for polio virus research in Copenhagen, Denmark in 1958, shipped from Singapore.[11] Monkeypox was first identified in humans in 1970 in the Democratic Republic of Congo in a 9-month-old boy during a period of intensified effort to eradicate smallpox. Following its recognition as a human pathogen, 59 cases of human monkeypox were reported between 1970 and 1980 in West Africa and Central Africa. Over the past 50 years, sporadic outbreaks have been reported mainly in African countries [12,13].

In 2003, an outbreak of monkeypox was reported in the USA infecting 53 people and was linked to contact with infected pet prairie dogs co-housed with infected Gambian pouched rats and dormice. Human monkeypox had never been reported outside Africa before [14]. In 2012, monkeypox virus was isolated from a dead infant mangabey monkey in West Africa. In October 2018, one case occurred in a man who traveled from Nigeria to Israel. In May 2019, one case occurred in a man who traveled from Nigeria to Singapore. In May 2021, a family returned to UK after traveling to Nigeria, and three family members became infected with the monkeypox virus [4,11,15,16].

On July 15, 2021, a case of human monkeypox was confirmed by CDC in a US citizen who traveled from Nigeria to Texas, USA. Another case was confirmed on November 16, 2021in a US citizen who returned to the Maryland, USA from Nigeria. In 2022 global outbreak surged with a new outbreak of monkeypox being reported in Europe in May. Cases related to this outbreak have continued to be reported in non-endemic countries worldwide, providing evidence of community spread. A total of 16.016 confirmed cases and 5 deaths have been reported from 75 countries from 1 January through 22 July, 2022. As of July 25 2022, four cases of monkeypox have been reported from India. The first three cases in India were reported from the Southern state of Kerala; all of them had travelled to the state recently from countries in the Gulf region. India's fourth case of monkeypox has been reported in a man in Delhi who has no history of foreign travel [4,11,17-19].

Transmission

Monkeypox is mainly transmitted via two routes –Animal to human and human to human. Animal to human (zoonotic) transmission can occur by the bite or scratch, direct contact

with body fluids or blood, cutaneous or mucosal lesions of infected animals. Eating inadequately cooked meat and other animal products is a possible risk factor [4,11,19].

Human to human transmission is by large respiratory droplets although prolonged face-to-face contact may be required, the possible reason why it might not spread as rapidly as influenza or Covid-19. Direct contact with infectious sores, scabs, body fluids, mucous membrane micro abrasions, indirect contact with fomites (clothing or linen) are some other ways by which one can acquire the infection [4,11,20].

The virus is able to cross the placenta from the mother which can lead to congenital monkeypox. In a report of four pregnant women with monkeypox from the Democratic Republic of the Congo, one gave birth to a healthy infant, two had miscarriage in the first trimester and one had fetal death with the stillborn showing diffuse skin lesions [21].

During the ongoing worldwide outbreak of monkeypox, close contact with the infectious material from skin lesions occurring during sexual activities is considered the main risk factor for acquisition. Curiously, vast majority of cases in the current May 2022 outbreak have been in men who have sex with men. The virus did not spread well between people in the past but may have found a new niche in tightly connected sexual networks [4,22,23].

A person is considered infectious from the onset of clinical manifestations until all skin lesions have scabbed over and re-epithelialization has occurred. In the light of this, decisions regarding discontinuation of isolation in both the health care facility and the community should be made in consultation with the local or state health department [4,11,18].

Pathogenicity and Clinical Symptoms

During the 2022 global outbreak, most patients with monkeypox have been symptomatic. Asymptomatic infection appears to be rare. Persons living in forested areas, male gender, less than 15 years of age, and not immune to smallpox are at increased risk of developing disease upon exposure to monkeypox virus [4,11,24,25]. Following viral entry, the monkeypox virus replicates at the inoculation site then spreads to local lymph nodes. Next, an initial viremia leads to viral spread to other organs. This represents the incubation period (interval from infection to onset of symptoms) and typically lasts 5 to 13 days but can range from 4 to 21 days. The disease begins with a secondary viremia leading to prodromal period that lasts 1-5 days. Initial symptoms include fever, severe headache, lymphadenopathy, back pain, myalgia, and severe fatigue [4,11,18].

The febrile stage is followed by the formation of a rash although rash without a prodrome has been reported. The rash tends to be more concentrated on the face but often develops on the palms and soles of feet and lasts 2 to 4 weeks. Other sites where rash can be seen include oral mucous membranes, conjunctiva, anus and genitalia. The rash evolves sequentially from macules (lesions with a flat base) to papules (raised firm painful lesions), vesicles (filled with fluid), pustules (filled with pus), and scabs or crusts which dry up and fall off. The number of lesions varies from a few to several thousand. In severe cases, lesions can coalesce until large sections of skin slough off. The lesions typically begin to develop simultaneously and evolve together on any given part of the body. However, during the global outbreak, not all lesions were in the same stage of development [4,11,24,25].

For most with efficient person to person transmission in both endemic and non-endemic countries individuals, Monkeypox is a self-limited disease with the symptoms lasting for two to four weeks. However, some patients may develop severe disease more commonly among children and immunocompromised patients. In recent outbreaks the case fatality rate has been around 3-6% [4,11,24,25].

Several rare complications of monkeypox include secondary bacterial infections, permanent skin scarring, bronchopneumonia, sepsis, encephalitis, conjunctivitis/keratitis ensuing vision loss. Nonspecific laboratory findings such as increased white cell counts, decreased platelet count, hypoalbuminemia and abnormal aminotransferase can be seen in patients with monkeypox [4,11,24,25].

The clinical presentation of monkeypox resembles that of smallpox, a related orthopoxvirus infection which was declared eradicated worldwide in 1980 (Figure 2). The basic difference is that monkeypox causes lymphadenopathy, but smallpox does not. Monkeypox is less contagious than smallpox and causes less severe illness [4,11,24,25].

Figure 2: Lesions of monkeypox on human skin [4].

Differential Diagnosis

Several infections need to be considered which may resemble the skin lesion of monkey pox such as chicken pox, molluscum contagiosum, herpes simplex virus infection, measles, syphilis, impetigo, rickettsial diseases, and drug associated eruption and clinical differential diagnosis is essential [4,11,24,25].

Diagnosis

The diagnosis of monkeypox should be suspected in patients who present with a rash or other symptoms consistent with monkeypox and epidemiological risk factors for infection including recent travel to Central or West Africa or other areas where large outbreaks have been reported [4,11].

A confirmed or probable diagnosis requires supporting laboratory evidence such as the detection of virus DNA testing using PCR. The optimal diagnostic samples are from skin lesions (roof or fluid from the vesicles and pustules and dry crusts, and biopsy is where feasible. Samples must be stored in a dry, sterile tube (no viral transport media) and kept cold. Cultivation in cell cultures is restricted to accredited biosafety level 3 reference laboratories [4,11,26].

As orthopoxviruses are serologically cross-reactive, serology and antigen detection methods may not be useful for diagnosis. However, Serological testing for monkeypox virus including detection of antibodies during the period of 4-56 days after onset of rash can be particularly helpful if viral DNA testing is not able to be performed. Persons who received smallpox vaccination may give false positive serological results [4,11,26].

Treatment

No specific clinically proven treatment for monkeypox. Most patients have mild disease and recover without medical intervention. Treatment is mainly supportive care and symptomatic management including fluid supplementation to prevent dehydration and proper diet to maintain adequate nutritional status. Additionally, Secondary bacterial infections should be treated with appropriate antibiotics [4,11].

Oral Brincidofovir [27] and cidofovir, [27] the oral DNA polymerase inhibitor, oral Tecovirimat, [28] a potent inhibitor of an orthopoxvirus protein required for the formation of an infectious virus particle and intravenous vaccine immune globulin have been approved for treatment of small pox and have demonstrated efficacy against monkeypox in animals [4,11].

Prevention

- Avoid contact with infected animals, as well as animals that are sick or have been found dead in the infected areas [4,11,29]
- Avoid touching any objects that have come into contact with a sick animal, such as bedding.
- Isolate infected patients from those who could be at risk of infection.
- After coming into contact with infected animals or humans wash your hands with soap and water or use an alcohol based hand sanitizer.
- When caring for patients, wear PPE.

Vaccination

The Modified Vaccinia Ankara (MVA) known by its trade name JYNNEOS is a smallpox and monkeypox vaccine, live attenuated, non-replicating vaccine with excellent safety has been approved for monkeypox and given in two doses subcutaneously, four weeks apart [4,11,30,31].

ACAM2000, replication competent smallpox vaccine can be only used in selected patients due to more adverse effects than MVA vaccine and is approved for the prevention of smallpox. It can be used for monkeypox under an expanded access investigational new drug application through the CDC [30,31].

Exposures in both community and health care settings should be monitored for the symptoms for 21 days after their last exposure. Vaccine as post-exposure prophylaxis if given between days 4 and 14 is thought to reduce the symptoms of disease but not prevent the disease [4,11,30,31].

In 2021, the Committee on Immunization Practices (ACIP) recommended the use of MVA vaccine as pre-exposure prophylaxis for certain workers at high risk of occupational exposure such as research laboratory personnel and clinical laboratory personnel performing diagnostic testing for orthopoxviruses [4,11,30,31].

Smallpox vaccine is 85% effective in preventing monkeypox. As a result of the end of routine smallpox vaccination, which provided some cross-protection in the past, people have become more susceptible to monkeypox [4,11,30,31,32].

Conclusion

Monkeypox is a zoonotic *Orthopoxvirus* infection that incidentally causes disease in humans similar to smallpox. This virus is clinically relevant because it is endemic to Western and Central Africa, with outbreaks in the Western

hemisphere related to the exotic pet trade and international travel. Health care professionals worldwide, particularly in non-endemic countries should become familiar with the clinical presentation and broader implications of this zoonotic viral infection, and update their knowledge in its prevention, clinical management, prophylaxis, basics of infection control, in light of contemporary outbreaks. Urgent actions must be taken to stop the virus to establish itself as a human pathogen with efficient person to person transmission in both endemic and non-endemic countries. More studies are still required to identify the exact reservoir and how virus is circulated and maintained in nature; and to understand the epidemiology, sources of infection, and transmission patterns. Although smallpox no longer occurs naturally, the global health sector must remain vigilant in the event it could reappear through natural mechanisms.

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