

Monkeypox: A Global Challenge

Sannia Perwaiz Iqbal^{1*} and Sajid Abbas Jaffri¹

¹Department of Family Medicine, Bahria University Health Sciences, Karachi, Pakistan

ABSTRACT

Monkeypox has emerged as the most significant human pathogen in recent times and is a rapidly growing threat to public health globally. Monkeypox virus is an orthopoxvirus, that belongs to the Poxviridae family. The smallpox virus also belongs to this family. Monkeypox virus, endemic to Central and West Africa can infect various animal species but can also transmit to humans. Monkeypox viruses circulate among wild animals and usually spread to people when they eat or have other close contacts with infected animals. Getting bitten or scratched by the infected animal, direct contact with its bodily fluids, blood, blisters or scabs; indirect contact with lesion material, e.g. contaminated bedding, linens and even eating the undercooked animal infected with monkeypox, could result in transmission. Among humans, Monkeypox is contracted through close physical contact, and contact with contaminated materials. Monkeypox presents with fever, headaches, myalgia, and enlarged lymph nodes. This is followed by a rash that starts from mouth to face and spreads to the trunk and arms. The illness is usually mild and patients fully recover within four weeks. Nucleic acid testing (NAT) is the primary diagnostic tool for detection. Polymerase chain reaction (PCR) is the preferred method for NAT. Treatment is mainly supportive and is directed to alleviate symptoms, prevent long-term sequelae and mitigate disease spread. Patients require isolation and symptomatic care. The smallpox vaccine, antiviral agents and vaccinia immunoglobulin (VIG) have been used in earlier outbreaks but sufficient evidence to recommend their use is still lacking.

Keywords: Monkeypox, animal diseases, poxviridae infections, orthopoxviruses, global health.

INTRODUCTION

Monkeypox is a viral zoonotic disease endemic in parts of Central and West Africa. The word “zoonosis” means that the disease can pass from animals to humans. Monkeypox can infect various animal species but can also transmit to humans [1]. The viruses generally circulate among wild animals and usually spread to people when they eat or have other close contacts with infected animals. Hunting, skinning, cooking or eating animals, or using products from an infected animal such as monkeys and rabbits, antelopes and gazelles, rodents, (rats, mice, squirrels), tree squirrels, etc [2]. Getting bitten or scratched by the infected animal, direct contact with its bodily fluids, blood, blisters or scabs; indirect contact with lesion material, e.g. contaminated bedding, linens and even eating the undercooked animal infected with monkeypox, could result in transmission [3]. Monkeypox is believed to be transmitted between humans *via* respiratory droplets and contact with contaminated materials. Unlike COVID-19, which spreads primarily through airborne transmission and the passing of small droplets, monkeypox is contracted through close physical contact. This includes prolonged face-to-face, skin-to-skin, mouth-to-mouth or mouth-to-skin contact such as kissing, cuddling, or sex [4]. Monkeypox was found to be more prevalent among homosexuals and bisexuals, indicating that the likelihood of spread of the virus through close skin-to-skin contact, such as sexual activities (oral, anal and vaginal), is considered to be high [5]. Monkeypox causes an illness

in humans that is similar to smallpox [6]. Smallpox is considered one of the most devastating diseases known to mankind and caused millions of deaths before it was eradicated in 1980. Smallpox was caused by the variola virus, a member of the orthopoxvirus family [7]. The clinical features of smallpox began with fever, aches and pains, fatigue and vomiting, followed by a skin eruption that starts from the mouth to the face and spreads to the rest of the body. The smallpox rash included painful fluid-filled blisters that would develop pus and eventually form scabs that crust off. The lesions would involve mucus membranes of the mouth and nose with painful blisters formation and ulceration. The disease was fatal in 30% of patients. Similar to smallpox, the telltale signs of monkeypox are also painful blisters that can develop throughout the body, however, Monkeypox has notably lower mortality than smallpox [8]. The illness is self-limiting, usually mild and most people fully within 2 to 4 weeks [4]. On 14 May 2022, a cluster of cases of monkeypox was reported from Europe. Since then many countries where no prior history of this virus have reported monkeypox cases.

The monkeypox outbreak was declared a global health emergency by the World Health Organization (WHO) On July 23rd. As of July 26, there have been 18,597 confirmed cases of monkeypox reported worldwide; and the case count continues to rise daily [9].

The recent outbreaks of monkeypox are different from earlier outbreaks which were related to a history of contact with animals or travel to endemic countries where monkeypox is found. Current areas with outbreaks include the United Kingdom, United States, Spain, Italy, Germany, France, Switzerland, Sweden,

*Corresponding author: Sannia Perwaiz Iqbal, Department of Family Medicine, Bahria University Health Sciences, Karachi, Pakistan; Email: sannapi@gmail.com

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Ireland, Canada, Saudi Arabia, Mexico, Australia, UAE, Israel, Morocco, Finland, Denmark, South Africa, Japan and many other areas that are non-endemic for this pathogen [10]. Monkeypox outbreaks outside of Africa have occurred in the past as well but have involved only a handful of patients with very limited local transmission [11]. Out of the more than 2,700 monkeypox cases recorded globally this year, 84% were in Europe, 12% in the Americas and only 3% in Africa [12]. The outbreak has mainly been in homosexuals and bisexuals [5]. The ongoing outbreaks of monkeypox in multiple countries are causing great concern among the general population [13]. The information flooding in about Monkeypox may be overwhelming. In this day and age, sorting out truth from exaggeration requires extensive expertise. The purpose of this review is to visit what the Monkeypox virus is, where it is found, how it is transmitted, how it causes disease, what the clinical picture is like and which complications it could give rise to. We will also discuss some important case definitions and learn how it is investigated, treated and prevented.

EPIDEMIOLOGY

History

Monkeypox was discovered in 1958 when outbreaks of an illness similar to smallpox occurred in colonies of monkeys in a research facility [14]. In 1970, the first human case of Monkeypox was detected in a 9-month-old boy from the Democratic Republic of the Congo (DRC) [15]. From 2001-2002, 485 Monkeypox cases and 25 deaths were recorded in the Democratic Republic of the Congo [16]. From 2017 to 2018, 122 cases of Monkeypox with seven deaths were reported in Nigeria. The incidence of monkeypox outside of Central and West Africa was previously considered to be rare [17].

Etiology

Monkeypox, belonging to the orthopox genus of the poxviridae family, is an enveloped double-stranded DNA virus. Smallpox (variola) and cowpox virus also belong to this family [3]. On electron microscopy, the Monkeypox virus is surrounded by a lipoprotein envelope with a linear double-stranded DNA genome. The virus has the shape of a brick and appears relatively large (200-250 nanometers) in size [4]. Poxviruses rely on host ribosomes for mRNA translation but have all necessary replication and transcription proteins in their genome [18].

Two main strains also referred to as the genetic clades of monkeypox have been detected, which include the Congo Basin or Central African clade and the West African clade. The Central African or Congo Basin clade is more virulent, causing more severe disease, and is less transmissible. Its case fatality ratio is documented to be as high as 10%. The West African clade causes a milder illness, is less virulent and less transmissible, with the case fatality reported to be around 3% [3]. Viral sequencing conducted in the UK found the West African

clade responsible for the recent outbreaks and seems to have originated from Nigeria [10].

Natural Host

The natural reservoir is unknown although many scientists suspect rodents play a part in endemic countries. Rats, squirrels, monkeys, prairie dogs, dormice, non-human primates and various other animal species have been found to be more prone to this virus [3].

Transmission

Monkeypox viruses generally circulate among wild animals in tropical rainforests but are increasingly becoming prevalent in urban environments. These viruses usually spread to people when they eat or have other close contacts with infected animals. Getting bitten or scratched by the infected animal, direct contact with its bodily fluids, blood, blisters or scabs; indirect contact with lesion material, e.g. contaminated bedding, and even eating the undercooked animal infected with monkeypox, could result in transmission. Monkeypox is believed to be transmitted between humans *via* respiratory droplets and contact with contaminated materials. Unlike COVID-19, which spreads primarily through airborne transmission and the passing of small droplets, monkeypox is contracted through close physical contact [19-22]. Monkeypox was found to be more prevalent among homosexuals and bisexuals, indicating that the likelihood of spread of the virus through close skin-to-skin contact, such as sexual activities (oral, anal and vaginal), is considered to be high [5].

Pathogenesis

The virus can enter from any route (oropharynx, nasopharynx, or through broken skin), and replicates before spreading to local lymph nodes. An initial viremic phase ensues, leading to the spread of the virus and seeding of other organs. This is the incubation period that usually lasts 1-2 weeks but can range from 0-3 weeks. The onset of clinical symptoms correlates with a secondary viremic phase in which prodromal signs such as fever and lymphadenopathy. The phase lasts a day or two before lesions appear. This is the contagious period. Lesions first appear in the oropharynx and then on the skin. The contagious period of the infection starts from the first day of symptoms till all the crusts of the rash have fallen off. Serum antibodies (anti-orthopoxvirus IgM) can be detected by the time these lesions appear [23, 24].

CLINICAL PRESENTATION

Signs and Symptoms

Monkeypox presents initially with fever, headaches, muscle pain, and enlarged lymph nodes. It causes a rash after a day or two, that starts from mouth to face and spreads to the trunk and arms. The illness is often likened to a milder form of smallpox, a disease that has been eradicated globally through widespread vaccination since 1980. Although scientists have shown

concern that the only way smallpox could re-emerge now is through bioterrorism [25].

The most commonly reported symptoms include rash (96%), followed by malaise (85%) and sore throat (78%). Signs elicited on physical exam include rash (99%); enlarged lymph nodes (98% – the cervical lymphadenopathy [85%] (see **Fig. 1**) inguinal lymphadenopathy [77%]); and mouth/throat lesions (28%).



Fig. (1): Cervical lymph node enlargement [26].

Course of Illness

Monkeypox infection is divided into two phases. The first phase or the invasion phase typically lasts anywhere between 0-5 days and is characterized by fever, chills, muscle aches, headache, backache, enlarged lymph nodes (lymphadenopathy), fatigue, malaise and asthenia (lack of energy) [27].

Lymphadenopathy is a characteristic feature of Monkeypox that helps distinguish it from other infections that cause a rash like smallpox, chickenpox and measles. Cervical lymphadenopathy is most common, followed by inguinal. The second phase of the disease is characterized by a skin eruption beginning within three days after the fever has subsided (see **Fig. 2**).



Fig. (2): Monkeypox lesions on the right hand and leg of a 4-year-old girl [28].

The rash has a centrifugal distribution, *i.e.* it begins from mouth to face and spreads peripherally to the extremities. This rash appears more on the face and arms than on the trunk. The rash evolves sequentially from macular to papular, then to vesicular, progressing to pustular and eventually forming scabs that crust off. Crusting off or desquamation occurs over a period of two to three weeks. Lesions vary in size from 0.5 to 1cm in diameter and the number of lesions can vary from a few to several thousand (See **Figs. 3-5**).



Fig. (3): Numerous skin lesions on the right arm and torso of a Monkeypox patient [29].



Fig. (4): Maculopapular rash on palms of a monkeypox patient [30].



Fig. (5): Recuperative Monkeypox rash in its recuperative (healing) stage on the dorsal surfaces of the hands of a monkeypox patient [31].

The face is affected in 95% of patients, 75% of patients develop lesions on the palms of the hands and soles of the feet, and 70% of patients report lesions on their oral mucus membranes. The genital region is affected in around 30% of patients, whereas the conjunctivae and cornea in about 20% of patients [32, 33].

Lesions starting in the genital area were reported in Europe and America in the recent outbreak [10].

CASE DEFINITIONS

A Suspected Case of Monkeypox is defined as:

An acute illness with fever $>38.3^{\circ}\text{C}$ or an unexplained rash and two or more other signs or symptoms like severe headaches, back and muscle pain, lymphadenopathy and severe lack of energy (asthenia).

A Probable Case is defined as:

A case that meets the clinical case definition, is not laboratory confirmed but has an epidemiological link to a confirmed or probable case.

A Confirmed Case is defined as:

A person who meets the suspected or probable case definition with laboratory confirmation (monkeypox PCR positive OR Isolation of monkeypox virus in culture).

Epi-Linked Case is defined as:

- Close contact with suspected, probable, or confirmed cases.
- Recent history of travel (within 21 days) to African endemic areas (Central and West African countries) [34].

DIFFERENTIAL DIAGNOSIS

Although a clinical picture is essential during an assessment, clues from patients' history can aid in building a differential diagnosis. The inquiry should be made regarding any history of travel or contact with imported animals from endemic regions.

Monkeypox rash must be distinguished from rashes caused by other conditions like chickenpox, smallpox, measles, syphilis, scabies, herpes simplex, chikungunya, dengue, rickettsia pox, chancroid, lymphogranuloma venereum, molluscum contagiosum, disseminated gonococcal infection, bacterial skin infections, vasculitis and drug-associated eruptions. Most often the rash is confused with the rash from chickenpox. However, differentiating features between the two diseases include that the rash in chickenpox progresses quicker, is more centrally located, and is in multiple stages of development. Moreover, patients with chickenpox neither have lesions on their palms and soles nor have lymphadenopathy, which is a key feature of Monkeypox [35]. Co-infection with monkeypox and chickenpox has a reported incidence of 10–13% [36].

DIAGNOSIS

For confirmation of Monkeypox, Nucleic acid testing (NAT) is the primary diagnostic tool for detection and skin lesions are the best source for collection of specimens. Polymerase chain reaction (PCR) is the preferred method for NAT.

Collection of specimens from at least 3 lesions on different sites of the body is preferred. Electron microscopy and viral culture can also be used, but are lower in sensitivity compared to NAT. Skin lesions are the best source for the collection of specimens. A biopsy is another option, wherever feasible Monkeypox patients may also develop laboratory abnormalities like increased white cell count and lymphocyte count, decreased platelets, elevated transaminases, decreased blood urea nitrogen and low albumin levels [37].

PROGNOSIS

Monkeypox is self-limiting, which means it can get better without treatment. In most cases, Monkeypox leads to a mild illness with patients making recovery in 2 to 4 weeks. The rash and pustules can last for several weeks.

However, severe cases have been reported, most commonly among young children. The case fatality ratio among unvaccinated young children is around 11%. Monkeypox during pregnancy can lead to complications including spontaneous abortion and stillbirth [38].

It is also necessary on the part of the health care workers to be aware of the signs and symptoms of Monkeypox for early recognition of cases and source control.

MANAGEMENT

Treatment

There is currently no proven cure for Monkeypox. Supportive symptomatic care and preventive measures are the mainstays of treatment. However, some medications can be used to control an outbreak and prevent the disease from spreading. The smallpox vaccine, antiviral agents and intravenous vaccinia immune globulin can be used to control the outbreak. Antiviral agents include brincidofovir and cidofovir, oral DNA polymerase inhibitors, and tecovirimat, an oral intracellular viral release inhibitor [39].

Tecovirimat (Tpoxx) is an antiviral agent used in the treatment of smallpox, monkeypox and cowpox. The drug was found to increase survival rates in animals given high doses of the Monkeypox virus. However, it is not yet widely available. In the USA it was only approved for treating smallpox [40].

Prevention

The main prevention strategy for Monkeypox is to educate people about the disease, its risk factors and precautionary measures to reduce their exposure and control its spread. Measures limiting disease transmission include proper hand hygiene, personal

protective equipment PPEs and environmental cleaning and disinfection.

Infection Control

Whenever handling suspected or confirmed cases, PPEs should be donned and doffed in the correct sequence (gowns, masks, goggles if splashes are expected, and gloves). Infection control measures include initiating airborne and contact precautions until chickenpox is ruled out.

Once chickenpox is ruled out, the patient should be shifted to a droplet with contact precautions. Whenever possible, all patients should be placed in a single negative pressure room [41].

Special Considerations

Strict adherence to standard precautionary measures is needed during the evaluation and sample collection of patients suspected of having Monkeypox. Personal protective equipment (PPE) which includes a gown, mask, goggles for eye protection and gloves should be worn by all health care workers.

In addition to standard precautions, suspected or confirmed cases should be placed under airborne, droplet and contact precautions [41].

Vaccination

Prior immunity to smallpox was found to be protective against Monkeypox. For health workers at risk, laboratory staff performing diagnostic testing for monkeypox, and all others who may be at risk, pre-exposure prophylaxis (PrEP) is recommended [42]. The smallpox vaccine is largely effective (85%) against monkeypox. The vaccine is made from a virus called vaccinia, which is a poxvirus similar to smallpox, but less harmful. Vaccinia virus is a large, complex, enveloped virus that is the source of the modern smallpox vaccine. Vaccinia immunoglobulin is immune globulin given intravenously to treat complications due to vaccinia vaccination [43].

Vaccina immune globulin (VIG) is composed of antibodies from individuals inoculated with the smallpox vaccine. VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency for which smallpox vaccination following exposure to monkeypox virus is contraindicated [44]. Jynneos also known as Imvanex or Imvamune is another vaccine approved by Europe and the US in people aged over 18, for the prevention of Monkeypox and smallpox. However, its availability is limited [45].

Ankara strain is a new vaccine that is a modified form of vaccinia recommended for smallpox and monkeypox. Ankara vaccine is recommended for post-exposure prophylaxis (PEP). When given within four days of exposure, it may prevent disease onset and if given within 14 days, it may reduce disease severity. Ankara vaccine has two dosages given one month

apart and is safer as compared to smallpox vaccines (vaccinia). In case of exposure to the illness, Post-exposure prophylaxis (PEP) with modified vaccinia, Ankara vaccine is recommended. Intravenous vaccinia immune globulin can also be used. Many countries have developed policies to offer vaccines to people at high risk of exposure such as healthcare providers, laboratory personnel and rapid response teams.

Mass vaccination is neither needed nor recommended at this time. The best defense against the worldwide spread of Monkeypox is through local containment [46].

Recommendations

The goal of treatment is directed to alleviate symptoms, treat complications, and prevent long-term sequelae. Screening and triage are recommended for all patients presenting with fever, rash or enlarged lymph nodes. Assessment of patients for the presence of severe disease and determination of any risk factors that could potentially lead to worse outcomes is critical.

Patients with mild, uncomplicated diseases can be isolated at home and should be counselled regarding signs and symptoms of complications that prompt urgent care. Patients require isolation and the treatment is mainly supportive. Adequate fluid hydration and diet are warranted.

Management of rash includes pain relief, monitoring for secondary infection, preventing complications, and hastening recovery.

Patients are considered at high risk for developing mental health illnesses such as depression, anxiety and other psychiatric issues. Prompt recognition through screening and appropriate treatment with first-line interventions and psychosocial support strategies for management of new anxiety and depressive symptoms or sleep disorders mental disorders is warranted.

Abstinence from sex is advised until all skin lesions have completely healed and a skin layer has formed. WHO recommends using condoms during all sexual activities. Young children, pregnant women and people with immunodeficiencies are more vulnerable to developing complications and may require hospital admission for closer monitoring.

Patients with severe disease or complications should be hospitalized where so they can be monitored closely and treated with optimized supportive clinical care interventions under appropriate isolation precautions.

Secondary bacterial infections should be recognized and treated as per standard protocol.

Complications such as skin and soft tissue infections require meticulous local wound care; whereas exfoliations may need surgical debridement and grafting. All patients should receive care that is patient-centered and maintains dignity, privacy and confidentiality [47].

COMPLICATIONS

Complications are rare but have been documented. Severe dehydration and electrolyte imbalances can occur due to loss of appetite, nausea, vomiting and diarrhea, or painful oral lesions. Moreover, subcutaneous fluid accumulation in the crusting phase of the disease can result in intravascular volume depletion, shock and death. Bacterial superinfection of skin such as abscesses, cellulitis, necrotizing soft tissue infections, sepsis, pneumonia, encephalitis and shock can occur. Cervical lymphadenopathy could give rise to a retropharyngeal abscess, respiratory failure and death. Corneal infections and permanent corneal scarring ensuing vision loss have also been reported. Other complications such as hyperpigmentation or hypopigmentation of the skin, permanent skin scarring, disfigurement and discoloration, pitted skin scars called 'pockmarks' [42-47] (see **Fig. 6**).



Fig. (6): Permanent pox mark scars on the face of a Monkeypox patient after recovery [48].

CONCLUSION

The recent outbreaks can be contained by contact tracing, like all outbreaks in the past. Guidelines and recommendations on how to mitigate the spread of Monkeypox worldwide are urgently needed as we can expect to find more cases of Monkeypox in the near future.

Surveillance needs to be expanded in countries where the disease is not typically found. It is imperative for health care providers to recognize the disease early, isolate patients and provide appropriate clinical therapy and mitigate disease transmission. Vaccination programs must be backed by thorough surveillance and contact tracing (household members or sexual partners).

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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