Review Article

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Monkeypox (MPOX): Unmasking the Lesser-known Viral Threat

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Abstract:

Monkeypox (Mpox) is caused by a viral infection and has been endemic in several African states after the last outbreak throughout the world in 2003. This disease resurfaced in the year 2022 and has since spread worldwide, even in countries where no cases had been reported in the earlier outbreak. While the world was still recovering from the menace of corona virus disease 2019 this virus; having similar features, started to spread across the world affecting thousands of people. The virus can be transmitted from human to human, and to humans from bites and scratches of infected animals. Common signs and symptoms include rashes and lymphadenopathy, accompanied with fever. Preventive measures for the Mpox virus include: using masks and alcohol-based hand sanitizers, practicing social distancing in crowded areas and practicing safe sexual activities. ACAM2000 and LC16m8 are a few vaccines available for its treatment. Early diagnosis and timely treatment of the disease have helped to curb the incidence and mortality of Mpox. Through this article, we discuss the history of infection, mode of transmission, the genomic data of the virus along with its signs and symptoms and its prevention and treatment using available vaccines. World governments and healthcare providers need to act appropriately in order to combat another such outbreak, as this disease has not been eradicated yet.

Keywords: IMVANEX, monkeypox, orthopox, rashes, smallpox, viral

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Introduction

The monkeypox (Mpox) virus has capsulated double-stranded (ds) deoxyribonucleic acid (DNA) and is classified under the genus Orthopoxvirus belonging to the family Poxviridae[1]. The virus is found to be brick-shaped with a dumbbell-shaped core, which is pleomorphic. The Mpox virus has 2 clades: the Central African (Congo Basin) and West African clades[2]. This genus also includes variola virus (the causative agent of smallpox), cowpox and vaccinia virus (VACV)[3]. Mpox is a zoonotic virus, which means it possesses the ability to cross and spread through different species. Various arboreal animals such as squirrels, rats and non-human primates are the natural hosts of Mpox, which explains the reason why it had earlier only spread in places having dense tropical forests like Africa. As a matter of fact it was firstly identified in captivated monkeys of the tropical rainforest areas in Africa.

This article intends to inform about the havoc caused by the virus, how and why it spreads and what are the management techniques and treatments available for it, giving the reader a basic overview of this disease. It is important for everyone to gain knowledge about this virus, because the danger is not over yet and the world should be ready for the next outbreak.

Material and Methods

We studied and revised nearly 60 articles and a multistep approach was used for the selection of articles, based on shortlisting of titles, abstracts and full texts. Keywords such as Mpox, outbreak, rashes and MPox mortality, were used for searches using online databases, including PubMed, Google scholar, Scopus and the National Library of Medicine, to retrieve studies. Articles providing the required details about the aforementioned subtopics were compared with similar articles, followed by extraction of data. The details have been cross checked in order to provide the readers the correct information concerning the topic.

History and current scenario

While the world is still facing the menace of the corona virus disease 2019 (COVID-19) pandemic, another threat has arisen for us: known as the Mpox virus. This virus was identified for the first time in the year 1958, in a laboratory in Denmark, when it caused an epidemic of pox-resembling illness in monkeys[4]. The very first human case of Mpox in humans was found in the Democratic Republic of Congo (DRC), in the year 1970[5,6]. Since the first week of May 2022, there has been an outbreak of this virus in countries where it was not endemic before[1]. A similar outbreak of Mpox occurred in 2003 as well, when it emerged in countries outside of the African continent; mainly in the United States[7,8].

Cases of the Mpox virus escalated in many countries; especially across the United States and Europe, which is different from what the world had seen earlier when the virus was limited to the countries of West and Central Africa. In outbreaks before May 2022, the Case fatality rate ranged from 3-6%[7]. The number of confirmed cases has decreased rapidly and as of mid-December 2023 new cases were recorded as around 26[9]. This is likely because a large number of the population across the entire globe are vaccinated against the smallpox virus, which belongs to the same genus of virus: Orthopox. As of the 19th of October 2023, a total of 91, 123 cases have been reported from 115 countries, resulting in the death of 157 people: as published by the World Health Organization (WHO)[10]. The health ministries of the affected countries have released certain guidelines for do's and don'ts to keep the contamination from spreading beyond control. The WHO declared Mpox as a globally concerning Public Health Emergency on the 23rd of July, 2022[11].

Mode of transmission

This virus can be transmitted to humans by scratches, bites, body fluids and meat of the infected animals[3]. A person with an infection is at a high risk of spreading

the virus to both their family members and healthcare providers in close proximity[12]. Mpox is not a sexually transmitted infection, although body fluids (like semen) do carry the virus and can cause an infection[13]. Certain groups of people like Men engaging in sexual activity with other men (MSM), People living with human immunodeficiency virus/acquired immunodeficiency syndrome (PLWHA) and the lesbian, gay, bisexual, transgender, queer, questioning, intersex, pansexual, two-spirit, asexual, and ally (LGBTQI+) community, are vulnerable[14]. This is because of physical contact with the body fluids (semen) of the infected person, which has a high chance of carrying the virus; however, since the disease can spread among people not belonging to the above-mentioned groups and from other sources (except semen, like mucous, faeces, etc.) it cannot be termed as a sexually transmitted infection (STI); like chlamydia, which spreads only through sexual contact. The fact that Mpox can spread only among people engaging in homogenous sexual activities is a misconception because the virus can spread to anyone in contact with an infected individual in any way (not necessarily sexual). The virus can enter the body through openings in the skin, the respiratory tract, and other means. The Mpox virus can spread from an infected person through direct contact or by exposure to their bodily fluids such as mucus, saliva as well as faeces[15]. Transmission from mother to foetus is also possible[3]. Complications of pregnancy include stillbirths, loss and preterm delivery in a few cases[3]. There are also chances of infection from any kind of sexual contact (like oral, vaginal, anal, etc.)[16], as traces of the virus have been found in semen samples, although absent in vaginal fluids[3]. The virus can spread through indirect contact, via lesions. It can also spread through the sharing of contaminated bed linens, towels, utensils or personal items. Whether or not asymptomatic individuals can transmit the virus is still unknown[3].

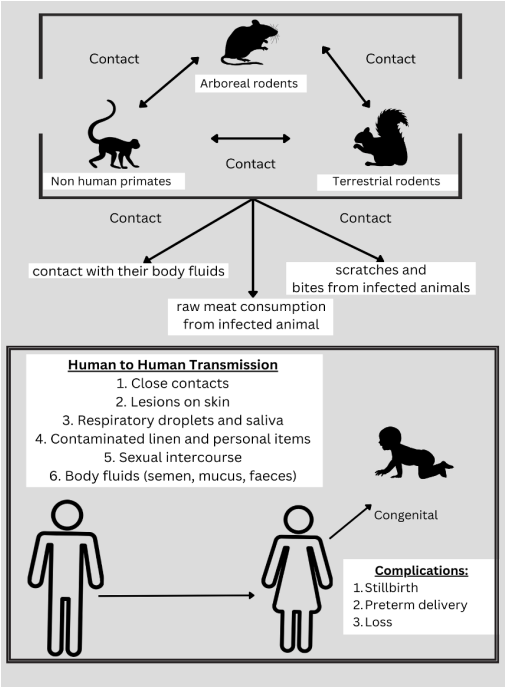

Figure 1 Transmission of the Mpox virus

Genomic data

It has been well established by laboratory diagnosis that the Mpox virus, a large dsDNA virus, causes symptoms that are indistinguishable from other pox-like illnesses; particularly smallpox (Variola virus) and chickenpox (Varicella virus), based on clinical observation alone.

Similarities

In 2001, similarities were drawn between the variola virus and the Mpox virus. Due to these emerging findings and continued scientific research, the concerns about using this virus as a tool for bioterrorism persist[17].

These two, distinct viruses can be distinguished through comparative genome analysis. There is a 96% sequence similarity in the genomes of the Mpox virus and variola virus. They share common orthopox ancestors, which infect rodents and ruminants, concluding that the

variola virus cannot be readily derived from the Mpox virus (or vice versa)[18]. They cannot be differentiated by neutralisation and haemagglutination inhibition[19]. These similarities cause difficulty in finding a definitive, reliable and rapid diagnostic test for Mpox. Only specific antisera can differentiate between the Mpox and smallpox viruses by means of specific viral antigens (mo and va respectively)[20].

Another trait common in smallpox and Mpox is that the virions contain over 30 structural and membrane viral proteins and virus-encoded DNA dependent Ribonucleic Acid (RNA) polymerase and associated transcriptional enzymes[21,22].

Differences

Even amongst the orthopoxviruses; the surface epitopes, polypeptide chains, cleavage site for DNA molecules and dsDNA genome, may still vary.

The Mpox virus expresses DNA polymerase (F8 protein), and it contains five domains; one large and four smaller units. The largest is named insert 2[23], this DNA polymerase holoenzyme contains processivity factors (A22-E4 heterodimers) and DNA polymerase.

Other poxviruses' genomes express DNA polymerase (E9 protein), with their processivity factors being heterodimers and made of A20 and D4 proteins[24].

Diagnostic use of genomic data

Approximately 90 Open Reading Frames (ORFs) are considered essential for morphogenesis along with replication. The non-essential ORFs help in the differentiation in poxvirus host tropism, pathogenesis and immunomodulation, with many ORFs still not being characterised as functionally. The characteristic genome feature of poxvirus particles is it having a dumbbell-shaped nucleoprotein core containing a singular large ds linear DNA genome[20].

The two live forms of mature poxvirus can be differentiated by measuring the levels of incorporated viral proteins. These two live forms are Extracellular Enveloped Virus (EEV) and Intracellular Mature Virus (IMV). While they are both capable of mediating the infection, EEV is thought to be responsible for early dissemination; whereas, IMV is released only during cell lysis[25,26].

Vitro studies on Mpox proved that this virus can affect most of the mammalian cells[27,28].

Mpox achieves cellular attachment through common glycosaminoglycan such as chondroitin and heparin sulphate, as well as laminin[29]. Therefore, proteins that control the biosynthesis of glycosaminoglycans play a major influential role in the mean platelet volume infection. This also proves that external factors influence the Mpox virus; such as virion proteins and cellular glycosaminoglycans on the surface of the target cell or the components of the extracellular matrix.

For the replication or DNA synthesis of the poxvirus, cytoplasmic structures called 'factories' (originally called Guarnieri bodies) exist[30,31]. They transform the compact form of DNA (containing structures wrapped by endoplasmic reticulum membranes) into a crescent-shaped structure where the virion assembly occurs.

It is well known that DNA genomes mutate less frequently than RNA viruses. This is due to the stability of double stranded DNA and the 3'-5' proofreading exonuclease activity of poxvirus DNA polymerase. In the Mpox virus, which has a double-stranded linear DNA, the adenine and thymine (AT content) is twice that of the guanine and cytosine (GC content)[32].

Ninety percent of the mutative editing in the ongoing outbreaks is handled by a family of enzymes called Apolipoprotein B mRNA Editing Catalytic Polypeptide-like (APOBEC3). In the 2022 outbreak, only seven mutations, out of the thirteen, resulted in amino acid change in the protein responsible for the viral transcription. However,

these mutations have not been shown to have any known functional impact on the Mpox virus[32]. APOBEC3 protein is also responsible for the entry and fusion complex formation single-stranded or double-stranded DNA binding inhibition of The Interleukin-1 (IL1) and Toll-like receptors (TLR) signalling and EEV envelopment[33]. In a study conducted in 2022, observation of a higher frequency of C to T mutations was recorded in the recently sequenced genome of the Mpox virus[34].

These binding and edition enzymes AOPBECs accelerate viral mutations by influencing the viral genomes and introducing a bias in genomic nucleotide usage. This influences cytosine metabolism and results in a decrease in C content and an increase in T content[32].

Natural defence and infection

After entry of the virus through respiratory or oral routes, the mucosa is invaded by this highly, extremely contagious virus. The first line of defence is innate immunity cells. Multiple in vivo and in vitro studies observed Poxviruses; including the Mpox, attack monocytes as their primary targets[35,36]. Monocyte and neutrophil levels can be used as early markers and can predict the lethality of the infection by detecting the presence of poxvirus antigens in them. Apart from monocytes and neutrophils, macrophages; B cells and dendritic cells are targeted[37]. Cynomolgus macaques show that monocytes accumulate at the site of infection and the lungs suffering from viral pneumonia show expansion of Cluster of differentiation 14 (CD14+) monocytes after Mpox infection.

In mice, Cluster of Differentiation 45 (CD 45+), Cluster of Differentiation 11b (CD 11b+) and Granulocyte Marker 1 (GR-1int) inflammatory monocytes have also been influenced from VACV replication and act as vehicles for virus dissemination[37].

In humans, primary M2-like macrophages help in VACV replication and dissemination. These primary macrophages form actin tails, cell linkages, lamellipodia and branching structures associated with VACV virions, following the infection. This proves that these cells help in the propagation of the virus[38].

To prove that despite the involvement of immune cells in the propagation, they are not the sole facilitators, as depleting immune cells in infected mice has been observed. It was noted that despite the lowering cell count, infection symptoms continued to increase. One study compared the low blood neutrophils to the fatality of the Mpox virus infected animals[39].

It is well established that CD4+ T cells enhance the memory B cells' differentiation into antibody secreting cells. The response of T cells against the Mpox virus was observed in HIV-1 patient; with CD+4 T cells count greater than 700 cell mm^3, and actively under the antiretroviral drug therapy. Mpox severity was markedly reduced in the patients[37].

The virus encodes several viral proteins that evade host immunity. They interfere with the signalling cascade of pathogen recognition. Ultimately, the symptoms of Mpox emerge in full force. This evasion occurs via many methods; including reducing cellular activation, targeting cytokine and chemokines, blockage of the complement cascade, escaping apoptosis and preventing IFNα/β signalling. The Mpox virus also blocks IRF3 signalling, PRR signalling cascade and NF-ΚB activation[37].

Signs and symptoms

The incubation period of the Mpox virus ranges from 5-21 days[7]. The mere presence of rashes is not sufficient to know whether the person has been infected with the Mpox virus or not because similar rashes occur in diseases such as bacterial dermal infection, chickenpox, measles or syphilis[40]. A characteristic sign for Mpox is lymphadenopathy, indicating the onset of the infection[41,42]. A Polymerase Chain Reaction (PCR) is preferred for testing

samples from lesions arising on the skin[7,43]. Onset of fever, date of collection of sample and patient's age is critical for the correct interpretation of test results[7]. India was the first country to develop an RT-PCR kit for testing the presence of the Mpox virus in samples[44].

This is a self-limiting disease[12]. The signs and symptoms vary gradually from the day of infection, and are generally noticeable 5-21 days after being infected[1]. The illness remains for 2 to 4 weeks[4]. After this the virus follows 2 phases: the invasion phase and the rash (or skin eruption) phase[1]. Initial stages of infection show symptoms much like those of chickenpox or smallpox, which include myalgia (muscle pain), fever, headache and abnormal physical weakness[17]. Later, the symptoms include lesions on the skin of the palm, mouth, genitals and rarely in the eyes[7]. As the days pass, the physical form of lesions show significant changes, from small flat spots to small bumps, which then fill with a clear fluid first, later changing to yellow fluid[45]. This bump eventually bursts, leaving a scab for about 10 days[46,47]. These scabs then leave a temporary dark scar on the skin[48]. An infected person may take about 2-4 weeks to heal completely[46]. The invasion phase of the virus (after 5-21 days of infection) causes symptoms like fever, chills, headache, myalgia, lymphadenopathy and hepatosplenomegaly[1]. About 5 days later, skin eruptions begin to appear, which mark the rash phase of the virus, making this a nearly 28-day cycle. The skin eruption phase is infectious, while the invasion phase is non-infectious[1].

A peculiar feature seen recently in the 2022 outbreak, is that the vast majority of cases were of men engaging in sexual activities with men, most commonly presented with ano-genital lesions[49,50].

The symptom severity of Mpox increases in immunocompromised individuals, pregnant women and people living with HIV/AIDS (PLWHA)[1]. It is assumed that advanced HIV infection can potentially increase the risk for prolonged viral shedding, increased severity of the disease and increased mortality[1].

The complications of the Mpox virus infection include inflammation of the brain and cornea and pulmonary manifestations in the form of pneumonia[4].

Generally, there are no long-term symptoms of the Mpox virus; however, some individuals have presented with disfigured and scarred skin as well as conjunctivitis[51-53].

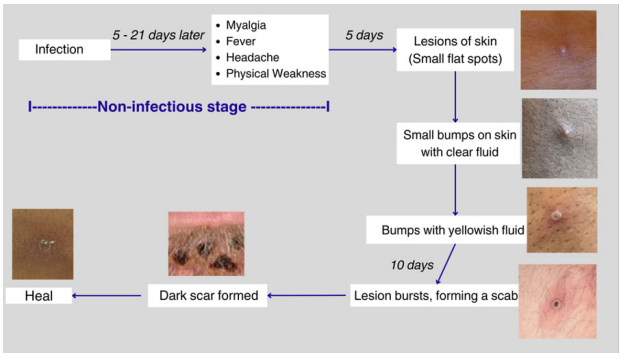

Figure 2 Rashes in Mpox[54]

Prevention and control

Previous vaccination against smallpox might be protective against the Mpox virus[55-56]. Healthcare centres should be well equipped with preventive gear, and if possible, a suspected case should be isolated until the results are reported. The patient should not only be isolated, but also be given a face mask or protective face shield, and if present the area of skin should be covered. Healthcare workers working for and around such patients should also take care of themselves by wearing masks and gloves, and by maintaining adequate distance from the patient[49]. Personal Protective Equipment (PPE); including a 3-ply face mask, gloves, full body gown, face shield/covers and boots, should be used by a healthcare provider while coming in contact/vicinity of an infected/suspected case. The room of the infected should be wet cleaned using a disinfectant, while using techniques like vacuum and dry dusting should be avoided as stated in the guidelines[1]. Isolate the infected person in a designated room if possible, otherwise, cohorts should be followed[46].

The preventive measures of the Mpox virus are quite similar to those of COVID-19, due to a similar mode of spreading. If a rash appears on the body, it is advisable for the person to be investigated by a physician and isolate themselves from their family/friends until they have absolutely recovered: doing so will prevent the virus from spreading and will help restrict the contamination. The WHO stated that the usual 3-ply mask, gloves, social distancing (around 1 metre), and washing hands with soap and alcohol-based hand sanitizers are the best ways to prevent this virus from spreading[57]. A person should not share any belongings of a suspected case like combs, utensils, bed linens etc. Sharing cigarettes should be avoided and practicing safe sexual activities should be encouraged[54]. Consumption of thoroughly cooked meat should be ensured[54]. Patients suffering from Mpox should be isolated in their homes in a room separate from the other members of the household and should be taken care of by a healthy individual; preferably one who has been vaccinated against smallpox[57]. The room should be well-ventilated. The WHO also recommends being cautious while handling bed-linens etc, of the rooms used by the infected individual and must be washed separately.

If pets come into contact with the Mpox virus, refrain from abandoning them, instead, isolate them and avoid close contact; particularly from pregnant women, children and immunocompromised individuals[58]. The pet should not be bathed or sprayed with a sanitiser, and a face mask should not be put over the pet's mouth and nose. International trading of animals should be checked[4]. The caretaker must be very cautious while handling the linens, toys etc. of their pet by wearing a PPE kit with mask and gloves[58].

Therapeutics and vaccine

Mpox not only resembles the clinical symptoms of smallpox but also responds to drugs in a similar way. Although no specified drug has been found for the complete treatment of Mpox, many antiviral therapeutics have the potential of relieving the symptoms.

Some therapeutics like Cidofovir and CMX-001, inhibit viral DNA polymerase and others; such as ST-246, inhibit, the release of intracellular viruses. The ST-246 drug mentioned above has proven itself remarkably effective on the variola virus[54,57]. They are commonly used in various combinations and their actions have been demonstrated on a variety of orthopox viruses. Vaccine-associated adverse events can be treated with vaccine immune globulin.

A few efficient vaccines are being used for Mpox. They are of two types; and ones that are only administered once. The examples are: ACAM2000 and LC16m[8]. ACAM2000 is a live VACV. It is contraindicated in immuno-compromised patients, patients with eczema or atopic dermatitis and pregnant females. LC16m8 is an attenuated VACV. It is considerably safer than ACAM2000[59]; however the latter is used for active immunisation and for individuals at high risk for contracting Mpox. Medical professionals handling vaccines, running diagnostic tests and interacting with patients of active Mpox virus infection are included in this. More data is explained in Figure 3.

The others require two doses: Modified vaccine Ankara, IMVAMUNE (US) and IMVANEX (Europe). These are live attenuated, non-replicating viruses and collectively called JYNNEOS[59].

Modified vaccinia, Ankara vaccine does not cause adverse cutaneous reactions. It promotes antibody formation even in patients with weakened immunity responses[60].

Apart from these vaccines many antiviral agents, originally approved for smallpox virus infections along with vaccinia immunoglobulin, are used for symptomatic relief. The three main antiviral drugs are: Tecovirimat, Brincidofovir and Cidofovir[58].

Conclusion

The threat for Mpox is not over yet, health care workers need to be educated enough about the virus for prompt identification, contact tracing, management and reporting new cases. Additionally, we should be prepared for its management and eradication.

CONTRAINDICATIONS	ACAM2000 (including both primary and re-vaccination)	IMVAMUNE/IMVANEX
Cutaneous complications	X	✓
Immunocompromised patients	X	✓
Cardiomyopathies	X	✓
Pregnancy	X	✓
Infancy (<1 year old)	X	✓
Breast-feeding women (including those with cardiomyopathy)	✓	X
Allergic (to the componenets of vaccines)	X	✓

Figure 3 Contraindications and uses of vaccines

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