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Commentary

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Out Foxing MPOX Virus (MPOXV)

Thyyar M Ravindranath, MD*

*Senior Lecturer, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Morgan Stanley Children's Hospital of NewYork-Presbyterian, Columbia University Irving Medical Center, Vagelos College of Physicians and Surgeons, 630 West 168th Street, New York, New York-10032, USA.

***Correspondence:**
Thyyar M Ravindranath, MD, Senior Lecturer, Division of Pediatric Critical Care Medicine, Department of Pediatrics, Morgan Stanley Children's Hospital of NewYork-Presbyterian, Columbia University Irving Medical Center, Vagelos College of Physicians and Surgeons, 630 West 168th Street, New York, New York-10032, USA.
Email: tr2148@gmail.com

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Abstract

MPOXV is a double-stranded DNA virus (ds-DNA) that recently caused widespread infection in humans. The eradication of smallpox and subsequent decrease or near elimination of vaccination against the smallpox virus resulted in a lack of herd immunity to the smallpox viral infection which then facilitated the resurgence of MPOXV. Two different clades of virus are described belonging to Central Africa and West Africa. The clade from Central Africa is more virulent, resulting in a higher mortality. In this commentary we describe epidemiology, genetic structure, mechanism of infection, the immune response, clinical presentation, differential diagnosis, complications, laboratory diagnosis, prevention, therapeutic options, societal outlook, and prognosis.

Keywords: viral infection, immunity, cytokines, vaccination, therapeutics, risk factors

Introduction

MPOXV is a DNA virus that belongs to the Orthopoxvirus genus within the Poxviridae family and the Chordopoxvirinae subfamily[1] and gives rise to an infection similar to smallpox. It is a brick-fashioned, oval shaped virus. MPOXV is a zoonotic infection endemic to Central and Western Africa seen in great numbers in The Democratic Republic of Congo. The primary host is unknown and is morbific in humans and in animals.[2] Animal reservoirs include rodents and other small mammal species.[3] Globalization has helped in the spread of MPOXV throughout the world including Asia and China.[4]

Epidemiology:

As of January 2023, the total number of cases reported were 84,716. Of these, the US reported 29, 980 cases. A worldwide mortality of 80 cases is known.[5] The highest risk is experienced in the Americas with moderate risk in Africa, the Eastern Mediterranean, Europe, and South-East Asia.[5] In the outbreak of 2022, males accounted for 96.8% of cases with a median age of 34 years as per the WHO, 2022 report. In Africa, pediatric patients accounted for 23% of MPOXV whereas it was less than 1% in the Americas and in Europe. The male to female ratio was lower in Africa. The secondary attack rate i.e., spread of infection in household, dwelling places, dormitory etc. over the past five decades ranged from 0% to 10.2%. The reproduction number (Ro), which is defined as the number of subsequent cases predicted to develop from a single initial case in a naïve population, was 2.44 (median) in the 2022 outbreak.[6] This suggests that human-human transmission was due to diverse promoting factors such as social behavior, different MPOXV variants, population density, and additional unknown causes.

Virological classification:

Two clades of MPOXV are identified, namely, the Western African and Central African (Congo Basin).[7] These are also described as Clade I (Congo Basin Clade) and Clade II (West Africa). Clade II is further classified as Clade II a and IIb.[8] Clade II b is further divided into A, A.1, A.2, A.3, and B.1 as per the Global Initiative on Sharing All Influenza Data (http://gisaid.org/). The Central African clade (Clade I) is more virulent, resulting in human-human transmission, viremia, morbidity, and mortality.[9] The mortality is 10% for the Central African clade(Clade I) versus 4% for the Western African clade (Clade II).[5] Overall, the mortality rate around the globe is 0.17%.[10]

Spread:

Viral spread can occur from animal to human (zoonotic) and human to human (inter-human). The most common mode of transmission to humans, however, is from the handling of infected animals or their secretions.[11] Person to person contact is fostered by living under the same roof or using the same utensils that an infected person had used, via respiratory droplets, contact with cutaneous lesions of an infected person or close interaction, living in countryside, deeply wooded areas of Central and Western Africa,

preparing and cooking bush meat. The other ways of transmission that were observed include hugging, kissing, oral, anal, and vaginal sexual intercourse.[12] Outside of Africa, the spread occurs following travel, contact with infected monkeys, and for population at risk for infection. Vertical transmission from mothers to their offspring can occur. No mortality was noted in vaccinated individuals. However, the mortality was 11% in unvaccinated adults and 15% in children.[13] The eradication of smallpox and the decline in its vaccination led to a loss of immunity against MPOXV. Susceptible hosts include immunocompromised individuals such as those with HIV, men having sexual intercourse with men, exposure to animal reservoirs, mass gatherings, and natural disasters.[14] Co-infection with varicella-zoster and chickenpox has been reported especially in children.

Genetic structure and mechanism of infection:

The MPOXV which is a double-stranded DNA (ds-DNA) with closely bundled genes, encoding 181 proteins. MPOXV ranges in size from 200-250 nm. It has a highly preserved central nucleoprotein core which is dumbbell-shaped, changing regions on the right and left ends, and end to end repeated inverted terminal. Clade I isolates have more uniform genome length versus Clade II. MPOXV undergoes viral invasion, reproduction, replication, assembly, maturation, and release. The virus replicates in the cytoplasm having a core area with lateral bodies in addition to ds-DNA and complete with a lipoprotein envelope. Viral entry occurs via ocular, nasopharyngeal, oropharyngeal, urethral, rectal, subcutaneous, intradermal, and intramuscular pathways and it's subsequent entry into the cell is enabled by pinocytosis, endocytosis, and cell membrane union. The virus can use lipid rafts on the lipid membrane to enter host cells, and cholesterol is one of the important constituents of the lipid rafts.[15] MPOXV attaches itself to broken skin and mucosa containing a high amount of glycosaminoglycans (GAGs), which functions as the principal attachment receptors for the host cells. Extra Cellular Enveloped Virus (EEV) react with GAGS and penetrate host cells. Marine sulfated polysaccharides, the natural equivalent of GAGs, prevent attachment and entry of MPOXV by competitive binding to the host cell membrane. There are many proteins on the surface of the intracellular mature virion (IMV) that may facilitate the entry of MPOXV into host cells via receptor and membrane fusion.[16] The spread of the virus is influenced by immune inflammation mediated phagocytosis at the viral entry site and results in further spread to the blood stream, lymph nodes, tonsils, bone marrow, spleen, as well as other organs. The spread may take two weeks, which constitutes a latent period. During the latent period individuals are asymptomatic without lesions. The latent period is followed by the release of genetic material and protein into the host cells under the command of mature virions (MV) and enveloped virions (EV). EV possesses an extra lipid layer externally aiding in the efficient intracellular spread of the virus. The final form of the IMV with DNA coding is produced by mRNA transcription and translation. IMV occurs in large numbers due to the lack of a lipid envelope, giving IMV a simple and tough structure that results in longer survival time outside the host. But at the same time IMV causes higher neutralizing antibodies, activating both complement system, and susceptibility to immune cells. However, the valosin-containing protein (VCP) of MPOXV inhibits the complement system and contributes to IMV's virulence. Intracellular enveloped virions (IEVs) develop following IMV's covering in Golgi apparatus by drawing a casing from Golgi membranes. Cell-associated virions (CEVs) are derived when IEVs fuse with inner host cell membrane. The subsequent release of CEVs into extracellular space results in the formation of EEV.[17] The replication of MPOXV is facilitated by uncoating the nucleocapsid envelope surrounding the central viral core of the EEV.[18]

There are other virulent factors of the MPOXV that protect lymphocytes from apoptosis and modulate inflammatory response to infection. These virulent factors produce interleukin-1β (IL-1β) binding protein which prevents IL-1β from interacting with IL-1 receptor (IL1R), perturbing innate and adaptive immune response and leading to virulence.[19]

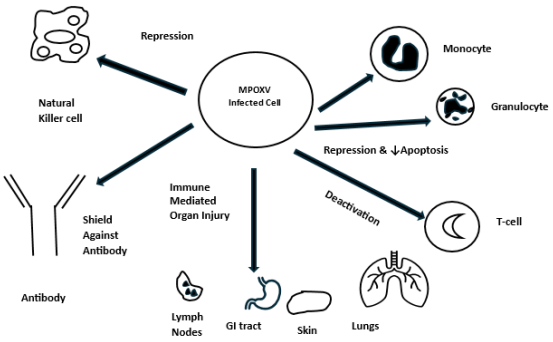

Figure 1: Immune Avoidance by MPOXV

Immune skirting of MPOXV involves inhibitory effects on NK cells, monocytes, granulocyte, and T-cells. It also results in multiple organ dysfuction especially involving the lungs, skin, gaterointestinal tract (GI tract), and lymph nodes. In addition, MPOXV protects itself from neutralizing antibodies.

Innate immune cells:

The immune cells are first line of defense against MPOXV. Initially, monocytes are recruited to the site of infection to quell the virus. The Natural Killer cells (NK) play an important role in producing a good immune response following infection. However, NK cell migration, degranulation, and the release of mediators are impaired by MPOXV, thus developing a strategy to avoid NK-cell mediated killing.[20] Dendritic cells (DCs) and innate lymphoid cells also undergo changes following MPOXV.[21] MPOXV can suppress chemokines 2 and 5 (CCL2 and CCL5) resulting in a decreased expression of downstream molecules such as IL-2, IL-12, IFN-ɤ, and TNF-α. Chemokine binding of MPOXV decreases the chemokine concentration gradient leading to suppression in neutrophil migration in infected tissues and resulting in suppressed inflammatory response as well as ensuing viral clearance

Adaptive immune cells:

T cells (Thymic), especially cytotoxic cells (CD8+ T cells) are effective in tampering disease severity through their mediators.[22] Suppression of immune cells lead to a decreased humoral response thus helping the virus evade immune system. Cytokine storm results from an increase in Th-2 (T helper) response and a decrease in Th-1 response. This gives way to an increase in proinflammatory cytokines such as IL-2, IL-4, and IL-8 and a reduction in TNF- and IL-12 thus leading to the disruption of host immune response.
T cell receptor (TCR) mediated T cell activation inhibition leads to a loss of anti-viral adaptive immune response. Interference with major histocompatibility complex II (MHC II) results in the loss of lymphocyte priming which leads to the forfeiture of anti-infective response. MPOXV rouses IgG and IgM antibodies, the long-term continuation of residual IgG memory B-cells, and an initial faster expansion of activated effector CD4+ and CD8+ T cells which is followed by a decline over the long haul.[23]

Gender and hormonal influences:

Males are more at risk for infection (≥50%) due to anti-immune effects of androgens as well as sex steroid hormones that have a negative effect on infection opposing genes.[24] Thymosin enhances immune responses of immune cells.[25]

MPOXV effect on cell signal transduction pathway:

MPOXV effect on signal transduction pathway has three major implications as follows: 1. Inhibition of pyroptosis which is an inflammatory program cell death characterized by swelling of the cells, membrane rupture, and the release of the proinflammatory mediators, is inhibited leading to interfering with immune response against the virus; 2. Inhibition of apoptosis defined as programed cell death leads to survival of MPOXV within the infected cells; 3. Interference with other signaling pathways results in the release of inflammatory, chemotactic factors , and alteration of immune cells.

The following discussion summarizes details of the molecular mechanism enunciated under major implications. The virus has the ability to disrupt apoptosis and pyroptosis pathways by inhibiting caspase-1 and caspase-8 via B-cell leukemia/lymphoma like protein (Bcl-2) and Salmonella pathogenicity island 2 (SPI-2) protein.[26] The other effects of the virus include suppression of host genes involved in the regulation of histone expression, cytoskeletal rearrangements, cell cycle progression, IFN-associated genes, and signaling pathways involving NF-κβ, mitogen-activated protein kinase (MAPK), and metabolic pathways.[27] Effective virus dispersion is accomplished by nerve growth factor inducible (VGF) protein. MPOXV inhibits Toll Like Receptor 3 (TLR 3) and TLR 4 signaling pathways preventing the generation of proinflammatory molecules and thus interfering with host anti-viral response and the ensuing activation of adaptive immune response.[28]

Clinical features:

The incubation period is 7-21 days. The long incubation period marks a difficulty in diagnosis thus delaying medical care and resulting in the further spread of the virus. Any history of travel to prevalent areas, interface with wild animals imported from endemic areas, taking care of infected individuals or animals helps in the diagnosis.

Symptoms:

Symptoms that are commonly experienced include fever, headache, muscle pain, back pain, chills, tiredness, and skin rashes.

Signs:

Signs of MPOXV virus infection comprise of breathing difficulty, ulcers that start in the mouth and then appear in the skin, face, extremities (including palms and soles) and are centrifugally distributed from a few to hundreds involving the throat and the GI tract, lymph adenopathy (which is absent in small pox), corneal infection, sepsis, and cellulitis. Clinical signs lasts two to four weeks.[11] The lesions evolve over 24-48 hours and go through macular, papular, vesicular, and pustular stages. These lesions form firm, deep seated lesions measuring 2-10 mm in size. Crust forms after about a week in the pustular phase. Crusts fall off after 7-14 days resolving in 3-4 weeks after the onset of symptoms. Individuals cease to be infective after the crusts fall off.[29] MPOXV directly infects injured skin and reproduces in fibroblasts, keratinocytes, and endothelial cells. Lymphadenopathy occurs 1-2 days before the appearance of skin rash. Inguinal lymphadenopathy was more common than in the cervical and axillary areas in the recent outbreak of 2023.

The virus has special affinity for organs such as ovaries, kidneys, heart, brain, pancreas, liver, and lungs.[30]

Differential diagnosis:

Differential diagnosis includes entities such as smallpox, widespread vaccinia, diffuse zoster, chickenpox, eczema herpeticum, herpes simplex, Rickettsial pox, drug eruptions, and measles [Table 1].

Table 1: Clinica Features of MPOXV vs. Differential Diagnosis

No.	Clinical	MPOXV	Differentia Diagnosis
1	Rash	With lyphadenopathy, pustules without fluid, lesions (new, healing, & healed) at the same stage of development.	**Varicella:** Without lymphadenopathy, pustules with fluid, lesions in different stages of development
2	Symptoms Confirmation	Oral & genital lesions, fever & myalgia more prominent	**Herpes Simplex:** Oral & genital lesions, fever & myalgia less prominent in recurrent cases PCR testing of the lesions
3		Non-golden crusts	**Impetigo:** Golden crusts secondary to bacterial coinfection
4		Macular, papular, vesicular, and pustular stages. These lesions form firm, deep seated lesions measuring 2-10 mm in size. Crust forms after about a week in the pustular phase.	**Molluscum contageosum:** single or multiple small, skin-colored papules with central umbilication
5		Lymphadenopathy is presenbt. Macular, papular, vesicular, and pustular stages. These lesions form firm, deep seated lesions measuring 2-10 mm in size. Crust forms after about a week in the pustular phase.	**Smallpox:** Lesions have deep-seated, firm/hard, round, well-circumscribed vesicles, or pustules. As a lesion grows, it could become umbilicated or confluent. Lesions are all in the same stage of development on one area of the body. The face and distal extremities contain the largest concentration of lesions in the centrifugal distribution of the rash, which is a diagnostic feature of smallpox.[38]

6			**Vaccinia virus:** Pustular lesions, may be confined to one or multiple parts. Accompanied by lymph adenopathy. Follows vaccination and direct trasmission of infection can occur to others [39]
7			**Other pox viruses** e.g., tanapox, Orf , and bovine stomatitis: Epidemiological charecteristics and exposure to animals helps to differentiade. Morphological features on electron microscropy helps to diagnose.[40]

No. = number

Complications:

Complications noted include bacterial superinfection, dehydration, skin scaring, hyper or hypopigmentation, vision loss from corneal involvement, encephalitis, hemorrhagic infection, necrotic lesions, inflammation of involved organs, and bronchopneumonia.

Laboratory diagnostic:

Diagnostic methods using skin lesion material from swabs obtained from surface lesions, exudates, and lesion crusts consist of, in brief, viral culture, electron microscopy visualization, immunohistochemistry, anti-orthopox virus IgG (signifying prior exposure or vaccination) and IgM (demonstrating recent exposure) 4-56 days after the onset of the rash, and real time PCR.[31] It is recommended to collect two specimens, each from several lesions from separate locations. The testing also includes checking for non-variola Orthopox virus.[32]

Prevention:

Contact tracing helps to control the spread of MPOXV infection. Those who are exposed to MPOXV must be monitored for 21 days assessing symptoms and are isolated to avoid passing on the infection to others.

Educating health care workers and patients about MPOXV is an important effective preventive strategy. The infected individuals must be isolated, wear a surgical mask, and keep lesions covered as much as practically possible until all lesions have crusted and fallen off with formation of new skin.

Other measures against MPOXV consist of vaccination using small pox vaccines, antivirals, or vaccinia immune globulin (VIG). Smallpox vaccine provides 85% cross-immunity against MPOXV due to shared antigens. Dryvax is a first-generation live replicating vaccinia virus vaccine and can cause severe infection such as progressive vaccinia. Two vaccines approved in the US include JYNNEOS which is a live-attenuated and non-replication vaccine (known as Immune/Imvanex in Europe) and ACAM2000 which is a live-attenuated and a replication vaccine.[33] JYNNEOS is not recommended for symptomatic individuals. ACAM 2000 allows the virus to replicate inside the cells resulting in serious side effects which include cardiac and painful skin reaction at the injected site and hence it is recommended only to high risk individuals such as military and laboratory research personnels. It is, however, not licensed in the European Union. In high risk exposure such as contact with an infected individual's body fluids, respiratory droplets or scabs, post-exposure vaccination is recommended within 4 days of exposure to prevent disease onset using a modified vaccinia, Ankara, which is a smallpox and MPOXV live and non-replicating vaccine. Disease severity is reduced when prophylaxis is carried out within 14 days of exposure. The Ankara vaccine is given in two doses 4 weeks apart with good results. The Ankara vaccine is not associated with skin lesions or local or distant spread and is safe in those with atopy and immune compromised states.[34] A third vaccine that is approved only in Japan is LC16m8 and is an attenuated vaccine.

Therapeutic options:

Mild infection needs only supportive management such as treatment for dehydration and analgesics for pain. For more severe cases such as in pediatric patients and pregnant women, as well as in immunocompromised hosts with lesions near critical areas such as eyes, genitals, and mouth, antivirals used against small pox are utilized. These consists of Tecovirimat, which is a viral release inhibitor administered by oral route, brincidofovir, and cidofovir.[33] Brincidofovir and cidofovir (acyclic nucleoside phosphate) inhibit viral polymerase. In severe cases tecovirimat can be combined with brinicidofovir. Normal saline and probenecid must be given concurrently with cidofovir to prevent injury to proximal tubules of the kidney. Cidofovir has low bioavailability. Brincidofovir, on the other hand, has higher bioavailability and is not nephrotoxic. It can however cause gastrointestinal and liver injury. Nucleoside analog Ribavirin blocks the synthesis of viral nucleotide inhibiting viral replication and spread. Ribavirin, in addition, functions as an immunomodulator by regulating T-cell polarization and promoting the release of IF-ɤ and T-box transcription factor (T-bet) resulting in the promotion of Th-1 response. Ribavirin also suppresses Th-2 response by inhibiting the release of GATA binding protein 3 and IL-4 favoring Th-1 response. Additionally, Ribavirin promotes the generation of central memory T cells and regulatory T cells (T regs).[35] As well, it promotes the release of IL-1β and IFN-ɤ via stimulation of NK cells and lymphocyte proliferation.

MPOXV induced cutaneous lesions can be treated with imiquimod topical cream. It has multiple effects that include an agonist effect on TLR-7 and TLR-8 resulting in the translocation and transcription of nuclear factor kappa beta (NF-κβ) which, in turn, leads to the release of proinflammatory cytokines enhancing immune response against the virus. It also directly enhances the production of IFN-ɤ, TNF-α, IL-1β, and IL-6 which induces a local innate immune response. Imiquimod also recruits dendritic cells (DCs) to the site of infection thus improving antigen presentation response.[36]

Corneal complications and infection spread can be prevented by the application of trifluridine eye drops which is a nucleoside analog.

Stigmatization and vaccine bias:

Sexual orientation and racial profiling are associated with MPOXV infection. Vaccine discrimination exists in lower and middle income countries. One needs to pay close attention and work against these biases through education of the general public and support.

Prognosis:

The West African clade has a favorable prognosis with a mortality rate of less than 1% whereas Central African clade causes a mortality rate of 11% in unvaccinated children. Most others make full recovery.[37]

Conclusion

Although the MPOXV infection, with its two clades, resulted in the widespread infection in the recent past, preventive strategies, vaccination of high-risk groups as well as education about the virus have resulted in the containment of its further spread. Vaccination bias and stigmatization needs to be transcended to further mitigate the spread of MPOXV. The focus must shift to aggressively educate the public and pursue preventive strategies in endemic areas.

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Author Contribution

Thyyar M Ravindranath, MD, planned, composed, and wrote the article.

Conflict of Interest

The author declares no conflict of interest.

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