Mechanism of Monkeypox Disease

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The past have witnessed an appalling rise in several emerging and re-emerging viral and zoonotic outbreaks. Such outbreaks are a lesson to learn from and seek insight into better disease monitoring and surveillance, thus preventing future outbreaks. Monkeypox, a viral zoonotic illness caused by the monkeypox virus, may no longer be endemic to the tropical rainforests of Central and West Africa. However, the monkeypox outbreak in nonendemic countries is most likely due to failure to curb the disease dissemination in endemic African regions despite constant outbreaks. The clinical manifestations are typified by a prodromal phase (fever, myalgia, malaise, and lymphadenopathy) followed by maculopapular or vesicular, or pustular cutaneous eruptions that eventually form encrustations and peel off. Children and the elderly, pregnant females, and individuals living with comorbidities (diabetes, HIV/AIDS, and lymphoproliferative ailments) are at a high risk of severe disease. Monkeypox is a self-limiting disorder, but its complications and pandemic potential signify its immense public health relevance. The ongoing monkeypox outbreak in nonendemic nations areas was identified with increased propensity in men who have sex with men (MSMs) with no travel history to endemic regions, emphasizing the changing trends in disease transmission.

monkeypox poxvirus public health menace

1. Taxonomy

Human monkeypox disease is caused by the monkeypox virus belonging to the Poxviridae family [1]. The family is subdivided into two subfamilies: Chordopoxvirinae and Entomopoxvirinae. The Chordopoxvirinae family primarily infects the vertebrates and is subclassified into 18 genera, including Orthopoxvirus. The Entomopoxvirinae subfamily infects invertebrates and is subclassified into four genera (Alphaentomopoxvirus, Betaentomopoxvirus, Gammaentomopoxvirus, and Deltaentomopoxvirus) [2].

The Orthopoxvirus (OPXV) genus has more than 10 member species, including the variola (smallpox) virus (VARV), vaccinia (the smallpox vaccine) virus (VACV), camelpox virus (CMLV), cowpox virus (CPXV), and several unique species isolated from infected humans or primates [3].

2. Transmission

Monkeypox infection primarily spreads via zoonotic and human–human transmission, usually through direct physical contact, a scratch or bite from an infected animal, or consumption of the host animal. Individuals with no smallpox immunization sleeping on the floor in recently deforested regions, and handling and consuming dead animals are more vulnerable to the zoonotic spread of the infection [4]. Respiratory droplet infection and direct contact with skin exanthem or scab lesions continue to be the principal modes of transmission between humans. Transmission may also occur by touching inanimate objects (clothing, beddings, etc.) contaminated with the virus, and the splashing or aerosolization of virus-containing particles when inappropriate biosafety procedures are undertaken [5].

Several monkeypox cases have been reported in men having sex with men (MSM). Some of these cases had documented international travel to nonendemic countries and attending mass gathering events or festivals, such as Maspalomas (Gran Canaria) 2022 Pride, thus suggesting a possible role of sexual intercourse that may aid in the transmission of the disease [6][7]. A recent study reported that the monkeypox virus detected in a patient's semen specimens during the acute infection phase might contain a replication-competent virus. The cytopathic effects observed after viral inoculation in the cell growth medium illustrate viral replication competency. Moreover, the authors proposed that monkeypox might have a genital reservoir as prolonged seminal viral shedding occurs, even at low viral copies [8].

Transmission can also occur via the fetus–maternal route (congenital monkeypox) or during close contact during and after birth [2][9][10].

3. Epidemiology

Historically, the monkeypox virus was first isolated in Copenhagen, Denmark in 1958 among imprisoned cynomolgus macaques imported from Singapore for research activities [3][11].

The first human monkeypox case was reported in 1970 in the Democratic Republic of Congo (DRC) when the region was thought to be variola-free and was under surveillance for smallpoxlike illnesses [3][9][12]. Since that time, DRC has been an endemic monkeypox region, although the virus continues to spread to other African countries, primarily in Central and West Africa [2][12].

Monkeypox cases were limited to the tropical rain forests of West and Central Africa, primarily due to close interaction with infected animals due to mass deforestation, the progressive fading of smallpox immunization, and ameliorated disease surveillance and diagnostic facilities in the African region [13].

Between 1970 and 1980, 59 cases were reported. A five-year period of active disease surveillance in DRC post smallpox eradication identified 338 cases [14]. However, the recent re-emergence outside of Africa poses the risk of identifying new risk factors. The first monkeypox case outside Africa was reported in the Midwest of the United States (2003), when exotic Gambian giant rats from Ghana infected prairie dogs, eventually infecting 47 human beings [2][9][15]. A monkeypox outbreak in Sudan accounted for a total of 10 confirmed and 9 suspected monkeypox cases from September to December 2005 [16]. In 2017, 122 documented cases in Nigeria showed both zoonotic and human–human modes of transmission [2][14].

Several isolated cases of monkeypox disease were documented in many non-African countries from 2018 to 2021, but they all shared a commonality in the history of travel to Nigeria: the United Kingdom reported 7 cases, Israel and Singapore reported 1 case each, and 2 cases were documented in the U.S [3][17]. In all the cases except one reported in the UK, human-to-human transmission was not detected [3][18].

Before the recent emergence of monkeypox disease in May 2022, epidemiological trends depicted that the disease occurred in individuals either with a travel history to endemic regions of Africa or those exposed to infected animals. However, in mid-May 2022, World Health Organization documented 257 laboratory-confirmed cases and approximately 120 suspected monkeypox cases in 23 nonendemic nations [19].

The recent monkeypox outbreak had an upsurge, particularly in men who have sex with men with no apparent travel history to the endemic regions [3][20][21].

By 22 September 2022, a total of 64,916 confirmed monkeypox cases were reported to WHO from 106 countries, of which 64,336 cases were documented in countries that have not historically reported monkeypox, and 580 cases in countries that historically reported monkeypox. Monkeypox cases were seen in 99 countries that have not historically reported monkeypox, and in 7 countries that have [22].

On 15 July 2022, the first case of monkeypox in the WHO Southeast Asia Region was documented in India, in a 35-year-old man who returned from the Middle East [23]. By 22 September 2022, 12 cases of monkeypox and 1 death were reported in India [11].

4. Pathogenesis

MPXV can invade human cells by the following modes: (a) direct integration between the molecules on the viral coat and the receptors on the human cell membrane [2][24]. Four viral proteins can facilitate the integration: D8 binds to chondroitin sulfate, A27 and H3 proteins bind to heparan sulfate, and the A26 protein binds to laminin [25]. The process of attachment is followed by the rapid dispersal of the viral envelope in the host cell membrane. Viral proteins and enzymatic factors are released in the cytoplasm, thus weakening the host defense and inducing the expression of early genes. Later, the formation of early proteins, DNA, and synthesis of intermediate transcription factors occur, with the (b) endosomal uptake through a macropinocytosis process involving actin [2][24].

Eleven proteins mediate the viral entry into the host cell. Nine proteins (A16, A21, A28, G3, G9, H2, J5, L5, and O3) are integral components of the entry fusion complex (EFC), whereas the other two proteins (F9 and L1) are EFC-associated [25]. Once it has gained access to the host cell, the monkeypox virus replicates at the site of inoculation before dispersing to the regional lymph nodes [26]. The monkeypox virus generates sufficient proteins for both transcription and replication, thus replicating within the infected host cell cytoplasm rather than in the nucleus, a contrasting feature with many DNA viruses [27].

This is followed by primary viremia causing the viral dissemination to other sites. This phase depicts the incubation period and ranges from 1–2 weeks to a maximum of 3 weeks. Prodromal symptoms such as fever and lymphadenopathy typically correspond with a 1–2 day phase of secondary viremia. Infected patients may be infectious during the secondary viremia phase. Lesions commence in the oropharynx, followed by skin eruptions [26][28].

5. Clinical Features

The incubation period of monkeypox varies in the range of 5–24 days, with a mean of 12 days [29][30]. Monkeypox virus infection typically describes a biphasic clinical presentation. A prodromal period of fever, headache, malaise, myalgia, and lymphadenopathy usually precedes the appearance of cutaneous rashes 2–4 days later [2][4][30][31][32].

Cutaneous lesions exhibit a salient pattern of progression, commencing as a well-defined exanthema that advances through macular, papular, vesicular, and pustular stages in a distinctive centrifugal pattern [3][5][9][15][27][31][32]. A typical rash lesion is vesicopustular. The lesions progress into papules by the third day, and vesicles (raised and fluid-filled) by the fourth to fifth day. By the sixth to seventh day, the lesions become firm, deep-seated pustules (sharply raised and filled with opaque fluid) that may umbilicate or coalesce. They eventually dry up and exhibit encrustations by the end of the second week, and the scabs exfoliate after a week. The lesions heal with hyperpigmented or hypopigmented atrophic scars, and patchy alopecia. Facial muscle contracture or deformity following healing of ulcerated facial lesions may also occur [33].

Lesions exhibit a site predilection, primarily affecting the face (95% of cases), followed by the palms and soles (75% of cases), and mucous membranes (70% of cases). The skin lesions infrequently affect the trunk and genitals [2][3][9][10][32]. On the basis of the number of lesions, the exanthem may be classified as mild (<25 skin lesions), moderate (25–99 skin lesions), severe (100–250 skin lesions), and very severe (>250 skin lesions) [34]. Scalp lesions were also reported in a few patients [15].

Severe monkeypox infections may present as encephalitis, pneumonia, secondary bacterial skin infection, and ocular diseases leading to keratitis, blurred vision, and corneal scarring, although most infections are relatively milder and self-limiting within 2–4 weeks. Neonates, children, and individuals with comorbidity and immunodeficiency are the most susceptible groups to infection [2][9][10][14][15][35][36]. Gastrointestinal symptoms such as vomiting and diarrhea may result in severe dehydration in an infected person. The dehydration may be further worsened with associated mouth and throat ulcers that may pose difficulties with maintaining nutrition. Sepsis and septic shock may primarily occur due to overly exaggerated immune responses [37]. Individuals coinfected with influenza may also present with bronchopneumonia [30][35].

There is a preliminary affirmation regarding a spectrum of neurological and psychiatric monkeypox presentations ranging from nonspecific neurological manifestations (such as headache and myalgia) to infrequent but more lethal neurological complications (such as seizures and encephalitis). However, there is a lack of conclusive evidence on the psychiatric sequelae and monkeypox-related nervous system presentations that may warrant surveillance within the current MPX outbreak [38].

The recent 2022 monkeypox upsurge has shown atypical symptoms in several cases. For instance, although the typical rash is still visible, it is usually limited to the genital, perigenital, and perianal sites, and displays different developmental stages. Additionally, patients may exhibit only mild or absent prodromal features, thus hindering the diagnosis and speedy quarantine of the patient. Therefore, it is imperative to encompass a wide array of disease manifestations for early and accurate diagnosis [32][39].

A recently published case series on 23 patients with a history of clear exposure during the current outbreak revealed that 95% of the patients reported a rash lesion (around two-thirds of the cases had <10 skin lesions). The frequency of the reported lesions was as follows: anogenital lesions (73%), mucosal lesions (41%), and a single genital ulcer (10%). The anorectal lesions caused severe anorectal pain in 11.5% of the patients, a feature not documented previously. Multiple types of lesions at the same time were also reported in the patients in the current outbreak, another distinguishing feature from the previous monkeypox outbreaks [40].

6. Orofacial Features

Dental professionals should remain watchful to the initial signs of a facial exanthem. Scrupulous steps should be taken to augment the knowledge among dental professionals regarding the presenting manifestations. As monkeypox infection may spread via short-range aerosol, dental professionals are particularly at a higher risk due to a large amount of aerosol-generating activity in dentistry [41]. Oral involvement in the form of a sore throat, oral ulcers, and dysphagia was reported by Gregory et al. [42]. Patel et al. reported oropharyngeal lesions, tonsillar erythema, pustules, edema, or abscess [9]. Oropharyngeal symptoms, such as pharyngitis, epiglottitis, odynophagia, and oral or tonsillar lesions were reported as the initial lesions in a few patients [40]. Rashes may be seen in the oral cavity, deteriorating the nutrition [31]. The occurrence of oral and throat ulcers, nausea, vomiting, and cervical lymphadenopathy during the early course of the illness may lead to a decreased appetite [35].

7. Diagnosis

Human monkeypox infection is usually diagnosed clinically with the characteristic skin exanthem. A comprehensive clinical history, including travel to endemic regions, occupation and contact with infected animals, and a confirmed laboratory diagnosis are imperative for differentiating the various rash-associated illnesses [27].

It is imperative to use personal protective equipment (PPE) during specimen collection. The specimen should be obtained from two distinct appearing lesions on distant body sites using sterile, dry synthetic swabs with plastic, wood, or a thin aluminum shaft (not cotton swabs). A sufficient amount of viral DNA may be obtained with vigorous swabbing, and unroofing the specimens may not be necessary nor recommended because of infection control or sharps injury concerns [43].

The polymerase chain reaction (PCR) test is the gold standard for a confirmed diagnosis of a suspected case. Certain real-time PCR assays can differentiate both the monkeypox virus from other orthopoxviruses and between two monkeypox clades [38]. Certain guidelines have been issued by the Government of India for the diagnosis of monkeypox infection. Samples including skin scrapings, EDTA blood, nasopharyngeal/oropharyngeal swab, and serum urine are processed for Orthopox genus-specific PCR. If positive, the specimens are further processed for monkeypox-specific PCR [44].

Biosafety Level 3 (BSL-3) containment laboratories should be used during the handling of any questionable infectious specimens. Due to its precision and credibility, GeneXpert was advocated as a potential diagnostic platform that may expand and hasten current MPXV detection abilities in endemic regions [27]. The specific benefits of GeneXpert and other similar point-of-care PCR platforms (e.g., TaqMans-MGB real-time PCR) may be more related to expanding the potential accessibility of testing and decreasing turnaround time.

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