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Research Article

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Monkeypox Infection, what we need to Know About

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Abstract

Monkeypox virus is an orthopoxvirus which was isolated for the first time in the 1950s from a group of unwell monkeys. It is in the same genus as variola that causes smallpox and vaccinia viruses. Although they are famously suspicious, there's no clear evidence that monkeys are the primary natural reservoir of the Monkeypox virus. However, humans and monkeys are considered to be incidental hosts. Monkeypox is usually acquired by humans through contact with animal fluid or bites, nevertheless, the human-to-human infection may occur through contact with infectious skin, exposure to large respiratory droplets and/or prolonged face-to-face contact within 6 feet for more than 3 hours without appropriate protections. Interestingly, the most recent outbreak that took place in May 2022 in non-endemic places has been linked to some sexual activities through an unknown mechanism. After the discontinuation of smallpox vaccination in 1979, monkeypox was endemic in Central and West Africa with sporadic cases reported in other non-endemic countries, mostly in returning travellers from endemic areas. In 2003, the United States of America reported an outbreak of monkeypox virus from infected prairie dogs who were in contact with imported animals from Africa. The incubation period of the monkeypox virus is 6 to 13 days with a range of 5 to 21 days. The most common presenting features of monkeypox are rash, fever, lymphadenopathy,

chills, and myalgias. It is usually a mild disease that might be associated with nausea and vomiting, and Most of the infected persons recover without intervention. However, more serious cases might require hospitalization and supportive care. Laboratory confirmatory tests are essential to differentiate monkeypox from fever and rash diseases. These include (i) virus isolation in mammalian cell cultures, (ii) direct electron microscopy, (iii) real-time polymerase chain reaction (PCR), and (iv) enzyme-linked immunosorbent assay (ELISA), and (v) immunofluorescent antibody assay. The public health authorities should be notified according to most states' health regulations. Varicella, smallpox, herpes simplex infection, and other orthopoxvirus infections are the differential diagnosis for Monkeypox. Tecovirimat and brincidofovir are the approved antiviral treatment for smallpox in the United States as their activity against monkeypox are approved in animals and are expected to be effective in human infection. Cidofovir has in vitro effect against monkeypox with a particular effect against lethal monkeypox in animal models. Contact, droplet, and airborne standard precaution measures are essential for any hospitalized patient with a generalized unknown vesicular rash as monkeypox and smallpox are part of the differential diagnosis. Pre- and post-exposure smallpox vaccination prophylaxis are reasonable options for select circumstances with appropriate notifications of public health authorities. In this review, we will discuss briefly the virology, geographic distribution, diagnosis and management of monkeypox infection.

Keywords: Poxviridae, Monkeypox Virus, Animal Monkeypox, Human Monkeypox, Epidemic, Smallpox Virology, Msm, Men Sex Men, Orthopoxvirus.

1. Introduction

Monkeypox is an infection caused by a zoonotic virus manifested clinically as a rash resembling a smallpox infection. Luckily, the mortality and human-to-human spread of monkeypox infection are considerably lower than that of smallpox. It is very difficult to differentiate between Monkeypox and smallpox only by their clinical presentations. There is a strong belief that the monkeypox virus-infected humans thousands of years ago somewhere in sub-Saharan Africa [1]. Monkeypox virus is an orthopox virus that was first identified in 1957 from a colony of sick monkeys in Toronto. It has the same genus of variola, which is the causative agent of smallpox, and the vaccinia viruses that were used for the smallpox vaccine. Monkeypox virus appears as a brick-like virion in the infected cells on electron microscopy. This feature is similar to the virions of variola or vaccinia.

Based on epidemiologic, animal, and molecular evidence, there are 2 distinct strains of monkeypox virus in various geographic regions of Africa [2]. The monkeypox virus of Western Africa is less virulent and lacks some genes of the other viral strain in Central Africa [2,3]. In the 1970s, in the Democratic Republic of Congo (previously the Republic of Zaire), the Monkeypox virus was first confirmed to cause human disease [1,4,5,6,7]. Later on, between 1970 and 1980, 59 cases of human monkeypox cases were described in the rain forests of Western and Central Africa among people exposed to small forest animals such as rodents, squirrels, and monkeys with a mortality rate of 17%. Years later, the first outbreak of the monkeypox virus took place in the United States of America in 2003 [8,9,10].

Humans are typically infected through contact with an infected animal's fluids or after an animal bite. Monkeypox virus infection has been identified in many types of African animals such as rope squirrels, tree squirrels, Gambian poached rats, dormice, and some species of monkeys [11]. However, monkeys like humans are not the original hosts; the permanent host remains unclear but is most likely to be a type of rodent. The infected rodents in Western Africa were accidentally brought which led to the first human monkeypox infections in the Western Hemisphere. The findings of a United States outbreak in 2003 showed that the route of infection and extent of exposure, bite versus the touch of the infected animal, might influence the severity of the monkeypox manifestations. Reynolds et al suggested that patients with complex exposures develop signs of systemic illness more likely than patients with non-invasive exposures [12].

Human-to-human transmission may happen through large respiratory droplets during prolonged face-to-face contact within a six feet radius for 3 hours or more without appropriate personal protection equipment (PPE) or through close contact with infected skin lesions or the lesion materials [13]. In general, transmissibility from person to person is very low [14]. However, in May 2022 an outbreak of monkeypox in several non-endemic countries was reported with many confirmed cases [15]. In this outbreak, close contact with infected skin lesions during sexual contact may be the likely mode of transmission [15,16]. Information that is more detailed will be available following further investigation. Additional information about this outbreak in specific geographic locations is found below.

2. Geographic Distribution

After the discontinuation of the smallpox vaccination program with the vaccinia virus vaccine following the eradication of smallpox, World Health Organization (WHO) monitored later human monkeypox movement. According to WHO experts that eradication of the vaccinia virus vaccine protects against monkeypox and, at the same time may increase the vulnerability of humans to monkeypox. Since the discontinuation of smallpox immunization, most cases have occurred in Central and West Africa. However, sporadic cases have been reported in several other countries, mostly related to travel. In the United States, there was an outbreak due to the importation of exotic animals from Africa.

May 2022 outbreak in non-endemic countries

The anxiety in May 2022 rises up from the occurrence of multiple clusters of monkeypox outbreaks in non-endemic countries in Europe and North America in men who have sex with men [1,2]. However, the direct human transmission may occur through

(i) large respiratory droplets, (ii) contact with body fluids, and (iii) contact with lesion materials. The most likely mode of transmission during the current outbreak was through close contact with infected skin lesions during sexual relations [1].

2.1 Africa

An outbreak of febrile disease associated with pustular skin lesions occur between 1996 and 1998 in 100 people with a secondary attack rate of 80% [4,7]. The concern during this outbreak was raised from possible mutation between monkeys and smallpox viruses [4,7]. Luckily, the assessment of the monkey pox in active cases showed no significant genetic changes in the Monkeypox virus [14,17]. The mortality rate in this outbreak was less than 5% indicating that monkey pox was not changed to a mutated lethal human disease [7,14]. A comparison surveillance study in the Democratic Republic of Congo between the 1980s outbreak and the 2005 to 2007 outbreak (760 confirmed human monkeypox cases) showed 20 times increment in the incidence of (incidence of what? And was it higher in the earlier or the latter outbreak?) This study confirmed prior concerns that persons with a history of smallpox immunization or exposure had a five times lower risk of monkeypox infection than unvaccinated or unexposed persons. Other risk factors include forest living places, male gender, and young age below15 years.

Nigeria showed increased monkey pox cases since 2017 after almost 40 years of no reported cases [19]. These cases may have resulted in monkey pox cases in travelers [20]. The WHO reported in 2022 that monkeypox was endemic in many African nations such as the Democratic Republic of the Congo, Benin, the Central African Republic, Cameroon, Gabon, Ghana, Ivory Coast, Nigeria, Liberia, South Sudan, and Sierra Leone. However, most cases appeared in the Democratic Republic of the Congo from January to May 2022 with 1238 cases and 57 deaths [15].

2.2 The United States and North America

From May till June 2003, 71 cases of human monkeypox outbreak occurred in 6 states for the first time according to Centres for Disease Control and Prevention (CDC) investigation. However, only 35 cases with laboratory confirmation by DNA sequences were obtained from skin lesions [8,9,10]. The onset of this outbreak started with febrile illness followed by a pustular rash in patients who had recently been in contact with prairie dogs. These prairie dogs were in contact with African rodents of two species housed at a distribution center in Illinois. Most of these human cases resulted from direct contact with animals [21]. However, direct human transmission was not excluded. The veterinary personnel who were in contact with prairie dogs were at the highest risk with an attack rate of 23% [22]. During this outbreak, the human transmission rate of monkey pox seemed very low [23]. However, the secondary attack rate for smallpox reached up to 70% [5,24].

After the prohibition of transportation, sale, and release of prairie dogs and animals (such as rope and tree squirrels, dormice, brush-tailed porcupines, striped mice, and Gambian giant rats) from Africa by the CDC and the United States Food and Drug Administration (FDA), no more outbreaks were reported in the United States [10]. However, individual cases have been reported (a patient with confirmed monkey pox in Dallas, Texas developed symptoms during his return from Nigeria in July 2021 [13]. Moreover, on May 18, 2022, another case was reported in Massachusetts that recently travelled to Canada using private transportation but did not travel to Africa [16]. Following that until the date of typing this report June 12, 2022, 48 confirmed sporadic cases were confirmed in the United States most likely related to a multinational outbreak of monkeypox [25]. A piece of Updated information on case counts in the United States can be found on the CDC website https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html. The reported and confirmed cases in Canada between May 2022 and up to the date of Incubation period the characteristic incubation period of monkeypox virus disease is between 6 and 13 days. However, it may range from 5 to 21 days [15, 32]. A shorter incubation period for patients with a history of animal scratches (9 days) or bites may have compared to those with tactile exposures (13 days) [12].

2.3 Clinical Manifestation

From the seroepidemiological studies done in Africa, the bulk of monkeypox cases are either mild or asymptomatic. In symptomatic patients, monkeypox lead to systemic manifestations such as fevers, chills, and myalgias, in addition to the characteristic rash that is masked with the rash of smallpox. Interestingly, the clinical presentation varies with viral strain. Descriptive details on the clinical presentation of monkeypox cases in Africa is found on the WHO and CDC websites were a rash that starts on the trunk and then spreads peripherally to reach the palms and soles. These lesions can occur on the mucous membranes which are ranging in size from 0.5 to 1 centimetre. This rash usually starts as macules and papules then evolves over the next 2-4 weeks to vesicles and or pustules, then umbilicated end with scabbing, and desquamation. Sometimes the rash appears as a solitary localized rash on the hands related to direct contact with the infected animal.

To overcome the scare of the comprehensive clinical details of monkeypox in Africa, the 2003 United States outbreak permitted further description of the disease in 34 of 37 cases [33]. The major signs and symptoms were: (i) rash in 97%, (ii) fever in 85%, (iii) chills in 71%, (iv) lymphadenopathy in 71%, (v) headache in 65%, (vi) myalgias in 56%. The fever preceded the rash by about 2 days with a median total duration of 8 days, which is shorter than the rash, which is 12 days. The rash during this outbreak was described to start as maculopapular then subsequently progressed into vesicles, then pustules, and finally crusted in a 2-3 week [33].

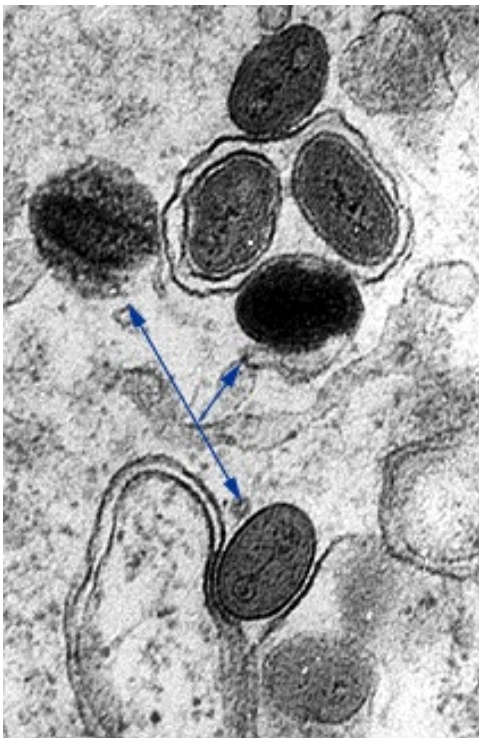
Out of the 34 hospitalized patients in Uthe SA, 9 cases had nausea, vomiting, and dysphagia. One of the serious discharge diagnoses of the 2 most seriously sick cases was encephalopathy and retropharyngeal abscess. The survival rate for this case series with appropriate supportive therapy was 100% without antiviral therapy. Other non-specific laboratory tests may show abnormal

liver function, leukocytosis, and/ or mild thrombocytopenia on complete blood picture (CBC), and hypoalbuminemia. During the May 2022 outbreak some patient presented with proctitis and other lesions of the genital or perianal area only [16,34].)

Diagnosis Laboratory confirmation is vital to differentiate suspected monkeypox cases from those caused by other potential etiologies. The WHO and CDC have set case definitions for monkeypox in the 2022 outbreak that consider clinical, epidemiologic, and laboratory findings.

Diagnostic assays include (i) virus isolation in cultures of mammalian cells in specialized laboratories, (ii) electron microscopy, (iii) real-time polymerase chain reaction (PCR), (iv) enzyme-linked immunosorbent assay (ELISA), and (v) immunofluorescent antibody assay [1,35]. The brick-shaped poxvirus virions characteristics can be seen on electron microscopy. The histopathologic analysis findings can also be seen in other viral infections which include (i) ballooning degeneration of keratinocytes, (ii) prominent spongiosis, (iii) dermal edema, and (iv) acute inflammation [36]. Using the 2003 USA outbreak patient's serum, the CDC established an immunoglobulin M-capture and an IgG ELISA to identify the recent monkeypox virus. The serum IgM was seen after 5 days while IgG antibodies were detected 8 days after the onset of rash [37]. There are few other under-development experimental antibodies and cellular-based assays which can be used for the prospective and retrospective diagnosis of monkeypox viral infection [24].

Poxvirus Virions



Electron micrograph shows intracellular brick-shaped vaccinia virions with dense central core and outer viral membranes (blue arrows). The electron microscopic image of variola virus would be identical to that seen here with vaccinia virus.

2.4 Notify local Public Health Authorities Should for Confined or Suspected Monkey Pox Is Being Considered.

• Differential Diagnosis

The differential diagnosis of Monkeypox viral infection includes (i) varicella, (ii) herpes simplex virus, (iii) smallpox, and (iv) other poxviruses. As smallpox was globally eradicated, the most possible differential diagnosis would be varicella (chickenpox). One important clinical differentiation between monkeypox and varicella is that all lesions are seen at the same stage in the first in comparison to different stages of development and healing in the latter. However, the concerns regarding bioterrorism make smallpox possible in the differential diagnosis of a patient not travelling to Africa or being in contact with potentially infected animals [6]. Lymphadenopathy is important finding in the majority of unimmunized cases, which is a key discriminative finding of monkey pox [10]. It may appear in the submandibular, cervical, or inguinal areas.

Another differential diagnosis is tanapox, an African poxvirus that produces a skin lesion after a febrile prodrome and resolves over many weeks without serious sequelae. One patient with tanapox viral infection was diagnosed by electron microscopy and PCR testing of a skin lesion biopsy in an American college student after working in the Republic of Congo for 8 weeks looking after chimpanzees [38].

3. Management

3.1 Supportive Care

The mildest infection recovers without medical intervention. Those with risk factors for the development of dehydration following nausea, vomiting, and dysphagia can be managed by a short course of intravenous (IV) hydration. However, supportive care is necessary for seriously sick patients to recover from the infection.

4. Antiviral Therapy

For mild, self-limited disease, antiviral therapy is not indicated. However, it may be practical to use antiviral therapy for severe cases with risk for serious disease consequences as in immunocompromised patients, children younger than 8 years of age, pregnant or breastfeeding women, and patients with complications of the infection [39]. Antiviral therapy is also indicated for monkeypox infection of atypical sites like the mouth, eyes, and genital area [39]. The antiviral therapy decision should be made in consultation with local public health authorities

4.1 The Following are Considered Immunosuppressed for the Purpose of Antiviral Therapy

(i) advanced HIV-1 disease, (ii) leukemia, (iii) lymphoma, (iii) generalized malignancy, (iv) solid organ transplantation, (v) therapy with alkylating agents, (vi) antimetabolites, (vii) radiation, (viii) tumour necrosis factor inhibitors, (ix) high corticosteroids dose, (x) recipient less than 2 years post-transplant of hematopoietic stem cell transplant, (xi) more than 2 years of graft-versus-host disease or disease relapse, (xii)

autoimmune disease with immunodeficiency [39].

5. Antiviral Therapy Agents

Some of the antiviral agents are approved for the treatment of smallpox based on animal trials with a dose tested in healthy individuals with an expectation to work against human monkeypox infection. Tecovirimat is the preferred treatment agent despite some experts may go with dual therapy of tecovirimat and cidofovir in severe cases after consultation with local public health authorities. Tecovirimat is a very potent inhibitor of the orthopoxvirus protein necessary for the formation of an infectious virus particle to disseminate into the infected victim cells. It can protect non-human primates from lethal monkeypox virus disease [40,41,42]. It seems to be effective in the treatment of Monkeypox human infection. It was approved for the treatment of smallpox in July 2018 by FDA [42] and the CDC [39]. There are oral and IV preparations for Tecovirimat. The advisable dose is based on the weight according to the manufacturer labelling for a duration of 14 days, and it is a well-tolerated medication. Headache, nausea, and abdominal pain are the most commonly reported side effects by approximately 360 out of ….. health volunteers in the safety trial with adverse effect profiles close to that of placebo [42]. However, the side effect might not appear in some patients [43]. Cidofovir is another antiviral agent that showed in vitro activity against monkey pox and had a good effect on lethal animal monkeypox [44,45,46]. Unfortunately, there are no data related to human monkey pox infection, especially since its use has been associated with serious side effects such as nephrotoxicity.

The brincidofovir medication was approved in the USA for the treatment of smallpox in June 2021 [47]. It is an oral analog of cidofovir with uncertain clinical availability with limited publication for its use in Monkeypox management in humans. However, animal trials showed promising effectiveness for orthopoxvirus infections [48,49,50]. Unfortunately, one of its serious side effects is the development of abnormal liver function at a dose of 200 mg once a week orally [43].

6. Prevention

Smallpox immunization

Prior smallpox vaccination with the vaccinia virus provides substantial protection against the acquirement of the monkeypox virus and may decrease the clinical features of the disease [5,24]. A modified vaccinia Ankara (MVA) vaccine was approved for the prevention of smallpox and monkeypox in September 2019 under the trade names Imvamune and Jynneos [51].

The Advisory Committee and Immunization Practices (ACIP) recommends the MVA vaccine for high-risk workers exposed to orthopoxvirus infection such as research laboratory personnel, laboratory personnel performing diagnostic testing for orthopoxviruses, specialized clinical designated response team members at risk of occupational exposure to orthopoxviruses, and healthcare personnel administering the live vaccine for active immunization against smallpox disease (ACAM2000) or care for patients infected with replication-competent orthopoxviruses [52,53]. The benefit of vaccinia virus smallpox vaccination is shown in data on monkeypox human-to-human transmission in Africa [23]. Another study demonstrated a fivefold lower risk of monkeypox infection as compared with unvaccinated persons in Africa [18]. The USA monkeypox outbreak was larger than previously realized some of the infected people may not present due to previous exposure immunity and the cross-protective antiviral immunity to West [24].

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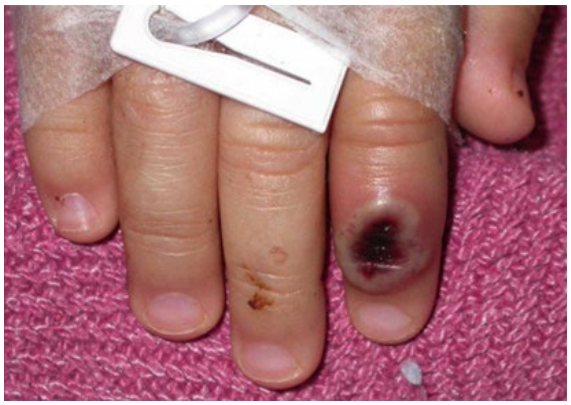
Child, marshfield index case



Primary inoculation site right index finger, 5/27/03. 14 days after prairie dog bites, 11 days after febrile illness, hospital day 5.

Figure 1. Schematic illustrations of the capsular and mulberry forms of the monkeypox virus.
A. The capsular form shows a sharply-defined dense core surrounded by laminated zones of differing densities; B. The mulberry form is covered by short, whorled filaments.
A. Capsular form
B. Mulberry form