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Monkeypox, a Re-emerging Infection: A Narrative Review

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Abstract

Monkeypox is a re-emerging infection caused by a zoonotic virus belonging to the Orthopoxvirus genus, same as smallpox and chickenpox. Since its discovery in humans in 1970, there have been outbreaks in African nations, the United States of America and Europe. The latest ongoing global outbreak has been declared a public health emergency. Traditionally, monkeypox has been a benign illness with spontaneous resolution in two to three weeks; however, atypical manifestations have raised concern for new challenges and fatality. No specific antiviral drug or vaccine is in current existence anywhere in the world. Vaccines for smallpox, antiviral drugs against viruses belonging to Orthopoxvirus genus and supportive treatment are the mainstay of therapy in the developed world. In the developing world, only supportive therapy is being employed. Vaccine development is in progress.

Key words: Monkeypox, re-emerging infections, monkeypox vaccine, smallpox vaccine.

Introduction

Humans have encountered infectious diseases since antiquity. But the agricultural age, which brought with it community dwelling and population growth, gave rise to conditions of new and continual microbial development[1]. Human intervention in the erstwhile wildlife has only accelerated these changes. Monkeypox is one amongst the many re-emerging infections. It has now been declared by the World Health Organisation as a global public health emergency on 23rd July, 2022[2]. Although so far a disease with low mortality, it is nevertheless a concern since it jumped out of its endemic zone in central and west Africa. Given the fact that the number of cases is on the rise everyday throughout the world, it is imperative for healthcare workers to apprise themselves of its clinical characteristics, transmission routes, preventive strategies, and methods of management. A brief discussion of other re-emerging infections is presented at the end.

Virology

Monkeypox is a deoxyribonucleic acid (DNA) zoonotic virus endemic to Central and West Africa. It belongs to the genus *Orthopoxvirus* of the *Poxviridae* family. It gets its name from the fact that it was isolated from laboratory monkeys in the 1950s in Denmark. The first human case was discovered in the Democratic Republic of Congo in the 1970s[3]. So far, two strains – Congo clade and West African clade – have been discovered. The current 2022 global outbreak is said to be the latter clade; however, it has been speculated that given its atypical presentation, it may be a new strain.

Transmission routes

Animal to human: Exposure via bites, scratches, body fluids and meat preparation can transmit the virus from animals to humans. Monkeys and humans are incidental hosts while rodents are suspected reservoirs.

Human to human: Amongst humans, it can spread through direct contact via sores, scabs, and body fluids. Soiled linens (fomites), prolonged respiratory exposure and vertical transmission has also been noted. It is not clear if semen and vaginal fluids are spreading agents, however in the 2022 global outbreak, viral DNA was discovered therein.

Clinical characterstics

Incubation period: It is usually 5 to 13 days with the range being 4 to 21 days.

Period of infectiousness: It is from the onset of clinical manifestations to the appearance of scabs and re-epithelialisation (appearance of new skin).

Signs and symptoms: It usually begins with a prodrome of fever, myalgia, severe headache, and lymphadenopathy. The prodrome can last for 5 days. About 1 to 4 days later, the characteristic rash appears which can continue for 2 to 3 weeks, followed by crusting in 1 to 2 weeks (Fig. 1). Rash without a prodrome has also been reported in the 2022 global outbreak. The lesions can range from a few to several thousands. It usually begins on the face and spreads centrifugally. Traditionally the lesions are synchronous but in the 2022 global outbreak, asynchronicity has been observed. Palms and soles, the oral mucosa, conjunctivae,

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and genitalia may also be involved. In severe cases, the lesions may coalesce and skin gets sloughed off. The lesion progresses from a macule, papule, vesicle to a pustule, followed by scab and culminating in the appearance of new skin. The rash is painful until it crusts (scabs), when it starts itching. It is usually a self-limiting infection.

Hospitalisation and case fatality: Hospitalisation rate is low with mortality for the Congo clade being 10% while it is 3 - 6% for the West African clade[4]. Mortality was not observed during the 2003 United States outbreak and in the current 2022 global outbreak, no death has been reported as of July 2022.

Complications: Secondary infections, bronchopneumonia, encephalitis, sepsis and *keratitis* which can lead to loss of vision.

Individuals at risk of severe disease:-

- Children younger than 8 years of age.
- Immunocompromised individuals (HIV-1 infection with

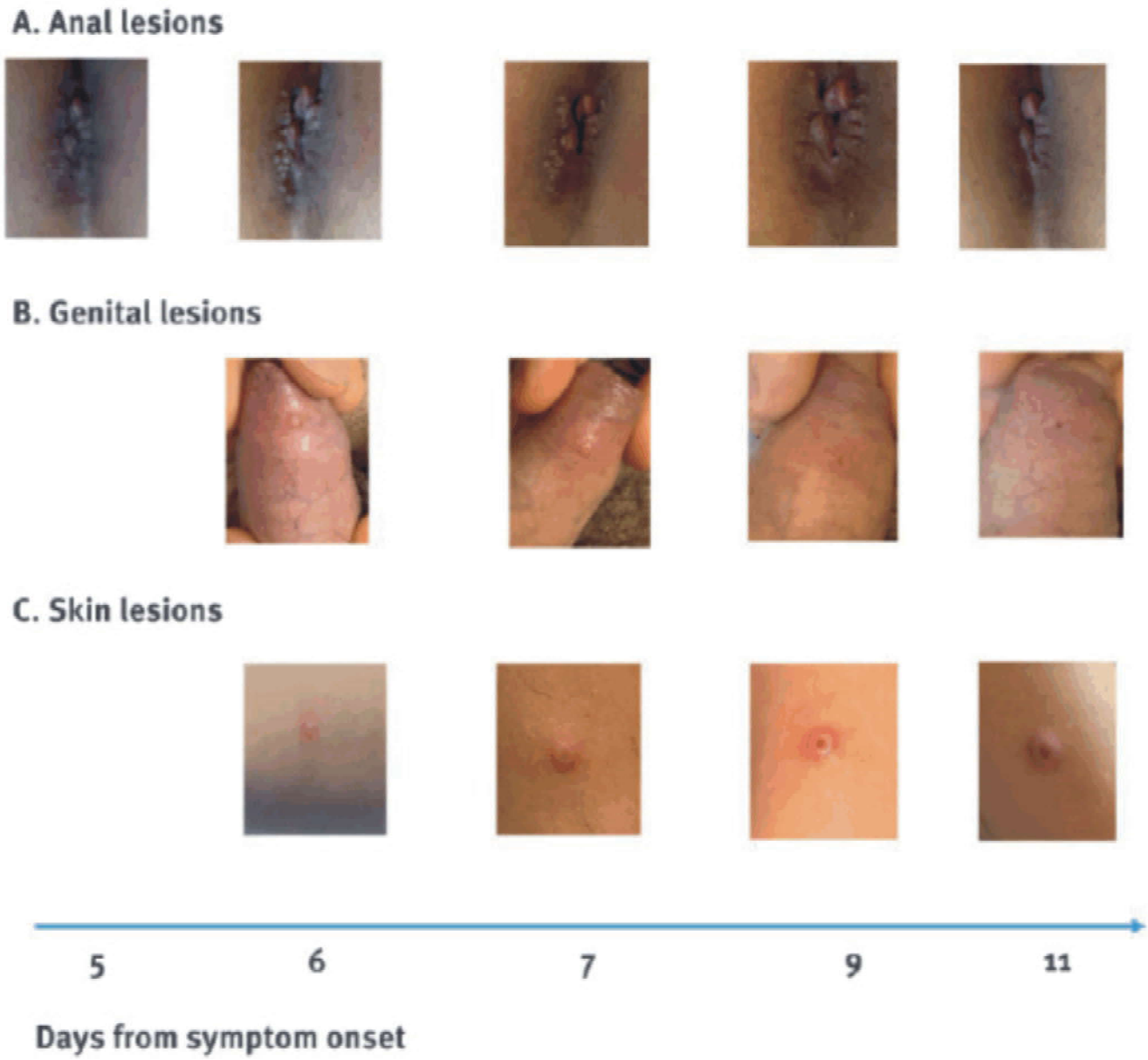

Fig. 1: *Stages of monkeypox rash. From: Antinori A, Mazzotta V, Vita S et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. Euro Surveill 2022; 27 (22). (Accessed on July 30, 2022). Reproduced under the terms of the Creative Commons Attribution 4.0 International License.*

clusters of differentiation-4 cell count < 200 per microliters), leukaemia, lymphoma, organ transplantation, ongoing cancer chemotherapy or radiotherapy, high-dose corticosteroids, haematopoietic stem cell transplant < 24 months).

- Exposure to high viral load.
- Presence of complications.

Caveats about the current 2022 global outbreak: In the current outbreak, certain atypical manifestations were observed such as the rash beginning in the genital area, rectal bleeding, rectal pain and tenesmus, asynchronous rash and a possible lack of prodrome.

Definitions

Contact history: A case is considered as indexed when s/he, within 21 days of onset of illness, came in contact with a probable or a confirmed case; or has traveled to an endemic country; or has come in contact with animal sourced from an endemic country.

Suspected case: Characteristic rash plus contact history; or genital ulcer or proctitis not responding to standard treatment for sexually transmitted diseases (STDs).

Probable case: Orthopoxvirus DNA detected by polymerase chain reaction (PCR), immunohistochemistry or electron microscopy; or presence of immunoglobulin M (IgM) antibody against orthopoxvirus within 4 to 56 days after rash onset.

Confirmed case: Monkeypox virus DNA detected by PCR or isolated in a culture.

Clinical exclusion criterion: Alternative diagnosis is satisfactory or there is lack of development of rash 5 days after symptom onset.

Sample collection, precautions and transport

Samples that can be collected: Rash roof, rash fluid, rash base or crust in plain tube, nasopharyngeal swab in viral transport medium, blood in yellow top tube (serology), blood in purple top tube (viral DNA).

Sample collection precautions: Samples must be collected in full personal protective equipment (PPE) comprising full body gown, N95 mask, face-shield, and gloves.

Sample transport instructions: Please refer to Ministry of Health and Family Welfare guidelines for detailed instructions[5].

Testing laboratory: As of the writing of this article, all samples are being sent to the National Institute of Virology, Pune.

Diagnosis

History: Travel to endemic region(s), past history of chickenpox, vaccination history, contact history including sexual history, pattern of rash development.

Diagnostic algorithm: As explained in the case definitions above, a two-tier system is in place for confirmation of monkeypox virus. Suspected cases are tested for the genus orthopoxvirus DNA via PCR. A test negative for orthopoxvirus DNA rules-out monkeypox virus. A sample that is positive for orthopoxvirus DNA (now labeled as a probable case) is tested for monkeypox virus DNA. If monkeypox virus DNA is found to be positive, it is now labeled as a confirmed case. IgM antibodies may also be tested in the blood specimen from 4 to 56 days after rash onset.

Differential diagnosis

It is important to be aware of common differentials that can be confused with monkeypox:-

1. Varicella (Smallpox):
   - It does not manifest with lymphadenopathy and has a characteristically asynchronous rash.
2. Herpes simplex:
   - Ideally only PCR can distinguish between the two viruses.
3. Herpes zoster:
   - Dermatomal distribution (widespread, if disseminated infection).
4. Smallpox (vaccine-associated).
5. Secondary syphilis, lymphogranuloma venereum, chancroid:
   - Since a portion of the individuals in the current 2022 global outbreak of monkeypox are those with sexual contact history, STDs should be kept in mind.
6. Hand-foot-and-mouth disease.
7. Measles.
8. Molluscum contagiosum.
9. Infectious mononucleosis.
10. Non-infectious aetiologies.

Treatment

Asymptomatic individuals with contact history: It can

take up to 21 days for symptoms to develop. Healthcare workers are advised to continue working, while keeping a lookout for the development of symptoms. Government guidelines for the general public are awaited.

Treatment at home: Patients who are haemodynamically stable, those who are not at risk of severe disease, non-pregnant females, and those without complications can be treated at home with supportive treatment as described below.

Criteria for hospitalisation:

- Severe disease.
- Individuals at risk of severe disease (see under Clinical Characteristics).
- Younger than 8 years.
- Pregnant or breastfeeding.
- Presence of complications.
- Immunocompromised individuals.

Patient isolation: Patient must be isolated, must wear a mask, observe cough etiquette, and cover all skin lesions.

Virus containment measures:

- Aerosol generating procedures in hospital must be done in PPE.
- Linen of patients must be handled with minimal shaking and ruffling.
- Standard detergent and water can be used for laundry.
- Use hand-sanitiser or soap and water for handwashing.

Supportive treatment

Skin rash: Patient must not scratch; local antiseptic and emollients can be used.

Genital lesions and proctitis: Sitz bath may be used.

Oral ulcers: Warm saline gargles may be used.

Fever, itching, dehydration, nausea, vomiting: Antipyretics, anti-histamines, antiemetics and fluids.

Antiviral drugs: None of the antiviral drugs are approved by the Centres for Disease Control and Prevention (CDC), United States of America (USA) specifically for the treatment of monkeypox (as of July 2022)[6]. However, certain drugs have been shown to have activity against monkeypox. Tecovirimat and cidofovir can be specially procured from the CDC for use against monkeypox (none of these are currently available in India).

1. Tecovirimat: it is an antiviral against viruses belonging to Orthopoxvirus genus. It targets F13 protein (for viral envelope), thus inhibiting the virus from developing an envelope and from exiting the host cell[7]. It is currently only available through special procurement from CDC, USA. Both intravenous and oral preparations exist. It needs to be given for a duration of 14 days. No major adverse effects have been reported. Oral drugs are associated with headache, nausea, and abdominal pain.
2. Cidofovir/brincidofovir: Cidofovir has shown *in-vitro* activity against smallpox, monkeypox, and cowpox[8]. Human studies are lacking. Brincidofovir is an oral prodrug of cidofovir. In a United Kingdom study on seven human monkeypox patients, tecovirimat/brincidofovir was used[9]. Three patients were treated with brincidofovir, all of whom manifested transaminitis. One patient who was given tecovirimat did not develop any adverse reaction and had a shorter hospital stay.

Monitoring for complications: Patients must be closely monitored for development of complications by paying attention to the following symptoms and signs:-

- Recurrence of fever after it has subsided previously.
- Foul smelling pus from lesions.
- Cough, shortness of breath, chest pain.
- Altered sensorium, seizure.
- Blurred vision, eye pain.
- Bleeding.

Preventive measures

Personal protection protocols:

- Facemask.
- Cough etiquette.
- Avoid crowded places.
- Avoid unprotected contact with wild animals, dead or alive.
- A suspected animal with contact history must be isolated for 30 days[10].
- Avoid sexual contact with multiple partners or with partner(s) with relevant contact history.
- Exchange contact details with sexual partner for retrospective contact tracing.
- Use condom during sexual intercourse.
- Do not touch lesions of patients with bare hands.
- Isolate self in case of doubtful symptoms.

Vaccination: No vaccine specific for monkeypox is available as of now. Vaccines used for smallpox are being

procured and stockpiled. NIV, Pune successfully isolated the virus in end-July 2022 and with the help of the Indian Council of Medical Research (ICMR), New Delhi has sought assistance of pharmaceutical companies to develop vaccines.

Post-exposure prophylaxis (PEP): As of now, there are two vaccines which may potentially reduce the risk of developing monkeypox post-exposure[11].

1. **Modified vaccinia Ankara (MVA):** It is a non-replicating, attenuated vaccinia (smallpox) virus vaccine which can provide cross-protection against monkeypox (both vaccinia and monkeypox viruses belong to the Orthopoxvirus genus). It is being manufactured as JYNNEOS in the United States and IMVANEX in the European Union. It can be administered to immunocompromised individuals. Two doses are supposed to be given subcutaneously four weeks apart.
2. **ACAM2000:** It is replication-capable vaccinia virus vaccine. It cannot be administered to immunocompromised individuals.
3. **Vaccinia immune globulin:** Immune globulin against vaccinia may be given to immunosuppressed individuals as PEP.

Emerging and re-emerging infections

Emerging infections (EIs) are those that have either never happened in humans or have occurred only in an isolated population. While re-emerging infections (REIs) are those that at one point of time were a major concern in a geographical area or globally; they declined and then reappeared as outbreaks[12]. Most EIs and REIs can be traced back to have originated from animals. Population expansion, urbanisation, globalisation, wildlife interference, among others are the reasons why viruses and bacteria which were previously confined to their ecological niches spilled over to exotic locations. Hosts – both animal and humans – who were never intended to be recipients of these ended up acquiring and transmitting these organisms, which now became pathogens.

In a 2007 article in *Nature*, Wolfe, Dunavan and Diamond enlisted five stages when a pathogen which exclusively infects animals (stage 1) transforms into an exclusive human disease (stage 5). A brief discussion of these stages with examples of pathogens sheds light on how these transformations take place. Not all pathogens reach stage 5.

Stage 1: Microbes exclusively present in animals and not found in humans under natural conditions.

Examples: Plasmodium malaria (most).

Stage 2: Microbes transmitted from animals to humans under natural conditions but not between humans.

Examples: Rabies, anthrax, tularemia, Nipah virus, West Nile virus.

Stage 3: Microbes that can undergo transmission between humans for a few cycles and that eventually die out.

Examples: Ebola virus, Marburg virus, monkeypox virus (historical trend).

Stage 4: Microbes that can undergo prolonged cycles of transmissions between humans.

Examples: Yellow fever, dengue fever, cholera, influenza A, typhus.

Stage 5: Microbes exclusive to humans.

Examples: Falciparum malaria, measles, mumps, rubella, syphilis, smallpox, diphtheria, tuberculosis, typhoid, human immunodeficiency virus.

Discussion of the evolution of these stages is outside the scope of this article. Suffice it to say that microbes at any given stage can travel to higher stages, given commensurate environmental conditions.

Conclusion

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease, monkeypox and other EIs and REIs have taught us a couple of lessons: human intervention inside biological diversity needs to be reigned in; preventive and management technology needs to catch up with mutating microbes, the unsuspecting healthcare workforce throughout the globe needs to be ever more cohesive to pre-empt pathogenic evolution of viruses, bacteria, and parasites. Expedited drugs and vaccine manufacture in the case of SARS-CoV-2 helped humans get back on track. We have already made strides in unveiling monkeypox genesis and progression. The future is likely to bring us similar challenges. In this regard, Ali Zumla (Professor of infectious disease and international health at University College London Medical School) is co-director of Pan-African Network For Rapid Research, Response, Relief and Preparedness for Infectious Disease Epidemics (PANDORA-ID-NET), a cross-continental strategy to deal with EIs and REIs[13].

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