Monkeypox: What do we know so far? A short narrative review of literature

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Abstract

Monkeypox virus (MPXV) is a zoonotic infection, first detected in parts of northern Africa in the 1970s. Monkeypoxvirus, the causative agent of monkeypox, is a species of genus Orthopoxvirus and is closely related to long-eradicated smallpox caused by variola virus. Outbreaks in the West (in USA, UK, and Ireland) along with periodic re-emergence of the disease in parts of Africa have generated concern among global health bodies due to the existing deficiency of guidelines for management of the disease. Genetic variations and altered mechanisms favoring better survival of the virus have made early identification of the disease during screening difficult, particularly in resource-limited settings like rural areas of Africa. Through evidences gathered from experimental studies conducted after these outbreaks, the virus is known to be transmitted from several animal reservoirs along with human-to-human contact of blood, body fluids, or aerosol. Early diagnosis through immunoassays and polymerase chain reaction (PCR) tests, although not very specific, allows early treatment and subsequently better patient survival and recovery. Presence of lymphadenopathy along with fever, sore throat, and a vesiculopustular rash is diagnostic. The virus affects the gastrointestinal, hematological, ocular, and respiratory systems, in like manner producing afflictions of the specific system. Treatment, through experimental data, has been preferred to be symptomatic, with the aim to prevent superinfections. Antivirals like cidofovir and tecovirimat have been studied upon and used in clinical trials with favorable outcomes. Antiviral immunoglobulins have also been used with success in certain patients for postexposure prophylaxis.

Introduction

Monkeypox virus (MPXV) is a zoonotic disease found sporadically in the tropical rainforest of central and western Africa with a considerable degree of threat to human life. It has been an emerging cause of frequent outbreaks in different parts of Africa in the past few weeks amidst the pre-existent COVID-19 pandemic. The geographic extent and status of the affected regions fail to bring the disease and the relevant news into global sight.2

There exist two genetic clades of MPXV, one is a Central African or the Congo basin clade found in the Democratic Republic of Congo, Gabon, Cameroon, Congo, and Central African Republic with a high level of infectiousness (up to seven generations) and a case fatality rate of up to 11%. The other is the relatively low infectious clade of Western Africa traced in Sierra Leone, Nigeria, Cameroon, Liberia, and Côte d’Ivoire with a case fatality rate of up to 6%.3

Transmission in humans can occur enterally through improperly cooked animal meat and parenterally through blood and body fluids secretion, mainly from the respiratory tract or skin lesions. A few distinctive symptoms of human MPXV may greatly aid in its early detection and containment.4 However, secondary transmission from imported cases of nosocomial transmission to a health care worker has been documented in the United Kingdom of Great Britain and Northern Ireland in 2018.5

Animal contact has also been a potential source of this disease.6 A study conducted in the late 1900s, proved that wild squirrels (species: Funisciurus anerythrus and Helosciurus rufobrachium) played a significant role in steady transmission of the virus.7 Epidemiological reports from the US outbreak of MPXV in 2003, proved pet prairie dogs housed with rodents imported from Ghana (Cynomys species) to be a potent animal contact, primarily responsible for the same.8 Additionally, in Africa, Gambian poached rats, dormice, and different species of monkeys have also been documented as the other possible animal contacts for MPXV transmission.9

Genetics and Pathogenesis
The genus Orthopoxvirus includes a number of viruses such as MPXV virus, vaccinia virus, variola virus, and cowpox virus. The genome of these viruses is ≈200 kb long with highly conserved central regions coding for replication and assembly machinery and more variable terminal ends that contain genes involved in host range determination and pathogenesis.10 Among these, MPXV virus has a relatively large genome made of the material needed for viral replication in cell cytoplasm causing pathogenicity in the host.11 The evolution of Orthopoxvirus has been postulated to be a result of progressive gene loss, particularly at the terminal end of the genome, which, along with gene copy number variation better viruses survival and fitness.12 Vaccinia virus homologs to genes found in the terminal ends of the MPXV genome are predominantly involved in immunomodulation, and most are either predicted or known to influence host range determination and pathogenicity.13 Additionally, MPXV virus bears four open reading frames in its inverted terminal repeats unlike other species of the same genus like variola virus.14,15

Genetic analysis and culture of virus with human cells and mouse cells separately showed the evasion of host innate immune system by virtue of MPXV bearing a suppressor of a full-length N-terminal domain on its E3 homolog, which allows full inhibition of protein kinase R (PKR) and allows replication in JC (a mitochondrial stain) indicator cells.16 The E3 protein is able to bind double-stranded RNA and sequester it away from known pattern recognition receptors (PKR, RIG-1, MDA-5, and OAS), thereby preventing their activation.17–19

Mice are spared from this mechanism due to the lack of a full-length E3 homolog which
limits the interferon response to the disease in them.\textsuperscript{20}

The histopathological analysis of skin lesions of MPXV showed similarity to other viral exanthems like cowpox, variola, varicella-zoster, and herpes simplex viruses along with ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation. Some keratinocytes showing large numbers of mature virions and immature virions in the process of assembly have been seen within the cytoplasm of infected cells.\textsuperscript{21}

**Diagnosis**

A preliminary diagnosis can be made based on a set of clinical evaluation criteria; it, however, must be differentiated from cowpox and smallpox due to the relative similarity in their presentation (Table 1). A definitive diagnosis can be made based on laboratory evaluation only. The available diagnostic assays for MPXV include virus isolation and electron microscopy, PCR, serum immunoglobulin M, and serum immunoglobulin G enzyme-linked immunosorbent assay, immunofluorescent antibody assay, and histopathologic analysis. The nonspecific nature of these tests makes it difficult to differentiate MPXV infection from other poxviruses.\textsuperscript{22}

A recent pilot of the Tetracore Orthopox BioThreat Alert provided promising results using lesion specimens from acute Orthopoxvirus infections. This assay reliably detected vaccinia and MPXV viruses in preparations with $10^7$ plaque-forming units/mL, and identified correctly five of six tested clinical specimens.\textsuperscript{23}

### Clinical Features

#### Skin

After a 10–14 days incubation period, prodromal illness with fever, malaise, and swollen lymph nodes is observed in most of the patients prior to the development of rash.\textsuperscript{24} The prodromal period generally lasts 1–3 days before the occurrence of the typical maculopapular rash, which starts on the trunk and spreads in a peripheral distribution to the palms and soles of the feet.

Lesions can be observed on mucous membranes, in the mouth and tongue, and on the genitalia. During the 1st week of the rash, the patient is considered to be infectious and should be isolated until all scabs separate and results of throat swab PCR are negative. The mean diameter of the skin lesions is 0.5–1 cm, and the clinical progress is very similar to that of ordinary smallpox lesions. During a 2–4 weeks period, lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation.\textsuperscript{25}

The pathology of these lesions intensifies as pustules form, with progressive ulceration, necrosis and epithelial hyperplasia, and prominent edema on the margins of necrotic areas. Development of clefts in the interstitial spaces between cells has also been noted. Later, apical evolution of the lesion with predominant inflammation and necrosis of the superficial dermis and destruction of sebaceous glands and follicles is evident.\textsuperscript{26}

Among patients with very high rash burdens (>250 lesions), interleukin-10, an anti-inflammatory, was markedly elevated which normally appears after the peak of illness severity, roughly coincident with the beginning of weight gain and recovery in the course of the disease.\textsuperscript{27}

Secondary infection at sites of compromised skin, or at breaches on mucosal surfaces, has been postulated to be the possible contributor of superinfections, cellulitis, or sepsis. Bacterial superinfection is hypothesized to contribute to scarring.\textsuperscript{28}

#### Lymph Nodes

Prior to and concomitant with rash development is the presence of maxillary, cervical, or inguinal lymphadenopathy (1–4 cm in diameter) in many patients. Enlarged lymph nodes are firm and tender. It is hypothesized that the presence of lymphadenopathy may be an indication that there is a more effective immune recognition and response to infection, favoring the diagnosis of MPXV since lymphadenopathy is not a prominent feature of other poxviruses (smallpox or variola virus).\textsuperscript{29}

#### Eyes

One of the most significant sequelae of MPXV infection is corneal scarring and concomitant loss of vision.\textsuperscript{30} In the previous outbreaks, stringent measures were taken to provide the affected individuals with ophthalmic lubrication, vitamin supplementation, and

### Table 1: Clinical features of different Orthopoxvirus species

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monkeypox</th>
<th>Smallpox</th>
<th>Chickenpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period, days</td>
<td>7–17</td>
<td>7–17</td>
<td>12–14</td>
</tr>
<tr>
<td>Prodrome period, days</td>
<td>1–4</td>
<td>2–4</td>
<td>0–2</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, severity</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild or none</td>
</tr>
<tr>
<td>Malaise, severity</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>Headache, severity</td>
<td>Moderate</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Lymphadenopathy, severity</td>
<td>Moderate</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth (diameter in mm)</td>
<td>Superficial to deep (4–6)</td>
<td>Deep (4–6)</td>
<td>Superficial (2–4)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Centrifugal (mainly)</td>
<td>Centrifugal</td>
<td>Centripetal</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Homogeneous rash</td>
<td>Homogeneous rash</td>
<td>Homogeneous rash</td>
</tr>
<tr>
<td>Time to desquamation, days</td>
<td>14–21</td>
<td>14–21</td>
<td>6–14</td>
</tr>
<tr>
<td>Frequency of lesions on palms or soles of feet</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Signs and symptoms of the diseases are not age-specific.

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88 | Journal of the Association of Physicians of India, Volume 70 Issue 7 (July 2022)
and tecovirimat have also been used with success for the treatment of MPXV. Studies using a variety of animal species have shown that tecovirimat is effective in treating Orthopoxvirus-induced disease. Human clinical trials indicated the drug was safe and tolerable with only minor side effects.38

A retrospective observational study conducted in the UK showed a decline in complications, days of hospitalization, and complete recovery of the documented seven cases in different parts of the nation over the past 3 years (2018–2021) with symptomatic disease management.39 Vaccination with smallpox is effective in prevention and postexposure prophylaxis of MPXV.40 However, in cases with contraindications to smallpox vaccines, the vaccinia virus immunoglobulin administered is equally effective as a means of postexposure prophylaxis.41

**Conclusion**

The periodic occurrence and frequency of such outbreaks bring to light the need of epidemic awareness, research, and preparedness. Although the availability of literature is limited, we must improvise upon research pertaining to the outcomes of conventional practices so as to devise specific, disease-modulating strategies to prevent transition to complications. Early detection and screening along with the available means of disease management can be helpful. Disparities in provision of healthcare facilities must be addressed in like manner, so as to permit better primordial prevention of the disease.

**References**