



Understanding Human Monkeypox: An Emerging Zoonotic Disease

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Abstract

Human monkeypox, a rare viral zoonosis endemic to central and western Africa, has recently emerged in the USA. Despite advancements in understanding its hosts and reservoirs, the primary reservoir for human infection remains unknown. The disease it causes is clinically similar to other pox-like illnesses, particularly smallpox and chickenpox, making laboratory diagnosis crucial. Various diagnostic tests can differentiate Monkeypox virus (MPV) infection from other poxviruses. However, serological testing for MPV antigens is challenging due to the close antigenic relation between surface antigens among the orthopoxviruses. Despite these challenges, understanding and diagnosing human monkeypox is critical due to its potential as a bioterrorism agent and its impact on immunosuppressed individuals, including those with AIDS. This review focuses on the clinical and epidemiological characteristics of human monkeypox, its hosts and reservoirs, and considerations for its diagnosis.

Introduction

Human monkeypox, a rare viral zoonosis endemic to central and western Africa, has recently surfaced in the USA. The disease it causes is clinically similar to other pox-like illnesses, particularly smallpox and chickenpox, making laboratory diagnosis crucial. The natural animal reservoir of the monkeypox virus remains unknown, but rodents are likely the source of its introduction into the USA. Our understanding of the virulence and transmissibility of human monkeypox is hindered by inconsistencies in epidemiological investigations. Since the eradication of smallpox in the 1970s, monkeypox has become the most significant orthopoxvirus infection in humans. Currently, there is no proven treatment for human monkeypox, and its potential as a bioterrorism agent remains a concern.

Following the global eradication of smallpox in 1977, the World Health Assembly has limited the maintenance of live variola virus to only two authorized facilities worldwide. However, recent concerns about the potential use of variola virus as a bioterrorism agent have brought the virus back into the public health and scientific research spotlight. These concerns have heightened the implications of any outbreak that clinically mimics smallpox, especially if caused by a novel or emerging agent. In the spring of 2003, an outbreak of a pox-like illness occurred in the central USA, attributed to the monkeypox virus (MPV), a rare zoonosis clinically indistinguishable from smallpox. This was the first reported occurrence of human monkeypox in the western hemisphere. This review focuses on the clinical and epidemiological characteristics of human monkeypox, its emergence in the USA, its similarities to smallpox and chickenpox, the potential of MPV as a bioterrorism agent, and considerations for diagnosis, treatment, and prevention.

Causative Agent

Monkeypox virus (MPV) is an orthopoxvirus, genetically distinct from other members of the Poxviridae family, including variola, vaccinia, ectromelia, camelpox, and cowpox viruses. It was first identified as the cause of a pox-like illness in captive monkeys at the State Serum Institute in Copenhagen in 1958. Monkeypox is considered the most significant orthopoxvirus infection in humans since the eradication of smallpox. Unlike variola virus, MPV has a broad host range, allowing it to maintain a reservoir in wild animals while occasionally causing human disease, thus preventing global eradication through human vaccination.

Signs and symptoms

The first case of human monkeypox was reported in a child in the equatorial region of the Democratic Republic of Congo (formerly Zaire) in 1970, nine months after smallpox was eradicated in that country. As cases in Africa increased in the 1970s, human monkeypox was thought to resemble smallpox in terms of symptoms, severity, and mortality. However, unlike smallpox, it was associated with low human-to-human transmissibility. As of 1980, fewer than 50 cases of human monkeypox had been recognized, and the clinical manifestations and epidemiology were not well characterized.

Most clinical data on human monkeypox come from subsequent investigations of outbreaks in central and western Africa. Observational studies in the mid-1980s showed an incubation period of 10–14 days and an infectious period during the first week of the rash. A characteristic 2-day prodrome, marked by fever and malaise, occurs in most patients before the development of the rash. In addition to the smallpox-like prodrome, severe lymphadenopathy occurs in many patients 1–2 days before the onset of the rash. Lymphadenopathy, not characteristic of smallpox, is a key distinguishing feature of human monkeypox. About 90% of patients infected with MPV develop lymphadenopathy, which can be unilateral or bilateral and occurs in the submandibular, cervical, postauricular, axillary, or inguinal lymph nodes, or any combination of these.

The typical human monkeypox rash begins as maculopapular lesions of 2–5 mm in diameter. Reports from African outbreaks suggest that the rash becomes generalized in most cases, spreading in a centrifugal pattern. A few cases have a centripetal rash, similar to that of chickenpox. The skin lesions typically progress through papular, vesicular, pustular, and crust phases over a period of 14–21 days, before sloughing and leaving dyspigmented scars. No hemorrhagic form of monkeypox has been described in humans. In addition to smallpox and chickenpox, other syndromes to consider in the differential diagnosis of a vesiculopapular rash include drug eruptions, eczema herpeticum, dermatitis herpetiformis, rickettsialpox, and molluscum contagiosum.

Hosts and Reservoirs

Despite advancements in understanding Monkeypox virus (MPV) hosts and reservoirs, many questions persist. Serological surveys indicate that various animals, including squirrels, non-human primates, and rats, are naturally infected with MPV. However, the primary reservoir for human infection is still unknown. Several studies from the Democratic Republic of Congo suggest that squirrels, particularly *Funisciurus anerythrus*, inhabiting agricultural areas, could be the primary candidates for sustaining viral transmission among people in nearby settlements. In one survey, *Funisciurus* spp squirrels had a higher rate of MPV seropositivity than other tested animals. A subsequent seroprevalence study showed even higher positivity rates in these squirrels. Additionally, 16% of tested Gambian giant rats had serological evidence of MPV exposure.

The establishment of an enzootic reservoir of MPV in the USA is uncertain. The infection of a rabbit after exposure to a diseased prairie dog at a veterinary clinic confirmed

the virus's transmissibility between common North American mammal species. This rabbit was implicated as the primary infection source in one US case. To prevent further MPV spread, the CDC and the US Food and Drug Administration issued a joint order banning the importation of all African rodents and prohibiting their transportation or sale. Despite these measures, concerns persist that the virus's rapid spread capability in rodents may have allowed it to establish a foothold in a US animal reservoir. An aggressive campaign to identify and quarantine or destroy the 800 mammals from the contaminated African shipment has been hampered by a lack of detailed records in many cases. If MPV has established an enzootic presence in the USA, the full implications are hard to predict. While previous analyses suggested that MPV cannot sustain itself in a human population, the possibility of frequent reintroduction from an animal source must be considered. For instance, the unusually large outbreak in 1996–97 in the Democratic Republic of Congo might have resulted from increased contact with infected animals by a displaced human community. High and sustained rates of MPV exposure might occur in other settings, such as the infection of wild rodent species in a metropolis like Chicago. The coexistence of high-density populations of people and animals such as rats, mice, and squirrels must be considered, as well as the potential consequences of human monkeypox in immunosuppressed individuals, including those with AIDS.

Diagnosis

Suspected human monkeypox cases should be reported to local health departments immediately. While clinical characteristics can help differentiate various poxvirus infections from other vesiculopustular rashes, laboratory confirmation is necessary for a definitive diagnosis. Suitable samples for diagnostic testing include cutaneous tissue and blood. At least two scabs or material from vesicles should be collected in separate sterile containers. The base of the vesicle should be swabbed with a sterile cotton or polyester swab, and the material applied to a clean microscope slide and air-dried. The material should be stored on dry ice or at -20°C for transport to the CDC (or equivalent national reference laboratory) for further diagnostic testing. Samples potentially containing monkeypox should be handled with Biosafety Level 2 practices, containment equipment, and facilities. Other clinical samples for diagnostic testing include skin biopsy tissue and blood. Biopsied skin lesions can be processed for future histopathological analysis and electron microscopy. Histopathologically, monkeypox lesions are indistinguishable from those of smallpox. Various diagnostic tests can differentiate MPV infection from other poxviruses. Currently, the CDC uses cell culture or chick chorioallantoic membrane isolation in conjunction with DNA-based assays for orthopoxvirus infection diagnosis. Serological testing for MPV antigens is challenging due to the close antigenic relation between surface antigens among the orthopoxviruses. Various serological methods are available, but their sensitivities vary, and they are not useful for diagnosing acute infection.

References

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