Reemergence of Monkeypox: Prevalence, Diagnostics, and Countermeasures

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Human monkeypox is a viral zoonotic disease that occurs mostly in the rain forests of central and western Africa. However, the disease recently emerged in the United States in imported wild rodents from Africa. Monkeypox has a clinical presentation very similar to that of ordinary forms of smallpox, including flulike symptoms, fever, malaise, back pain, headache, and characteristic rash. Given this clinical spectrum, differential diagnosis to rule out smallpox is very important. There are no licensed therapies for human monkeypox; however, the smallpox vaccine can protect against the disease. The discontinuation of general vaccination in the 1980s has given rise to increasing susceptibility to monkeypox virus infection in the human population. This has led to fears that monkeypox virus could be used as a bioterrorism agent. Effective prevention relies on limiting the contact with infected patients or animals and limiting the respiratory exposure to infected patients.

Human monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV), a member of the genus Orthopoxvirus (family Poxviridae, subfamily Chordopoxvirinae). Other notable members of this group include variola virus (the causative agent of smallpox) and vaccinia virus (the virus used in the smallpox vaccine). Less well-known members include ectromelia, camelpox, and cowpox viruses. Human monkeypox is clinically almost identical to ordinary smallpox, and therefore, since the global eradication of smallpox in 1977, much attention has been paid to monkeypox as a smallpox-like disease and possible agent of bioterrorism. Additional attention was brought to bear on this virus when, in the spring of 2003, it emerged for the first time in the Western Hemisphere and caused a cluster of cases in the US Midwest. This article will review the current state of knowledge about human monkeypox, with emphasis on epidemiologic characteristics, clinical features, diagnosis, treatment, and prevention.

EPIDEMIOLOGIC CHARACTERISTICS

Monkeypox in Africa. Monkeypox has presumably occurred in sub-Saharan Africa for thousands of years, ever since humans acquired the virus through direct contact with infected animals. The reservoir for MPXV is still unknown. However, there are data to suggest that monkeys are, similar to humans, incidental hosts, and that the reservoir is likely to be 1 or numerous species of rodents or squirrels that inhabit the secondary forest of central Africa [1]. Monkeypox was not recognized as a distinct disease until 1970, when the elimination of smallpox from Zaire (the present Democratic Republic of Congo [DRC]) revealed the continued occurrence of a smallpox-like illness in rural areas. Widespread vaccination in central Africa during the global eradication campaign presumably caused a temporary reduction in the incidence of human monkeypox, but the absence of immunity in the generation born since that time and the increased dependence on hunting for food in areas devastated by civil war have resulted in reemergence of the disease.

Initial epidemiologic studies conducted during 1970–1979 detected a total of 47 cases of human monkeypox near rain forests of sub-Saharan Africa, of which 38 occurred in the DRC and the remainder in Cameroon, the Central African Republic, Gabon, Cote d’Ivoire, Liberia, Nigeria, and Sierra Leone [2, 3]. All cases in the DRC occurred in areas bordering tropical rain forests and appeared to be associated with animal contact. Seven of the 47 reported infections were fatal. Secondary transmission was determined to be the most likely cause of infection in 4
cases, with secondary attack rates of 7.5% among close family members living in the same household and 3.3% among all susceptible contacts. Since 1980, the vast majority of cases have continued to be reported from the DRC.

To determine whether monkeypox had the potential to emerge from central Africa and occupy the niche vacated by smallpox, the World Health Organization conducted an active surveillance program from 1981 through 1986 in the DRC, where 338 of the 404 recognized cases in Africa occurred during 1970–1986 [4]. An animal source of infection was suspected in 245 of the 338 cases, and secondary transmission from a human source was presumed in the remaining 93 cases. The majority of cases occurred in children, and the mean age of patients was 4.4 years. These increases in the secondary transmission rate (3 times the 9% rate for cases in the 1970s) and the age distribution were thought to reflect waning immunity since the discontinuation of vaccination. The longest documented chain of infection consisted of only 4 generations of person-to-person transmission, indicating that MPXV had little potential for epidemic spread [5]. Serological surveys involving vaccine-naive children that were undertaken during this period found that 12%–15% of participating children had antibodies against MPXV, but most did not have a history of compatible illness, suggesting that subclinical infection also occurred [4]. Since the end of the World Health Organization surveillance program in 1986, to our knowledge, only a handful of articles in the medical literature have described the continuing occurrence of human monkeypox. During 1986–1992, only 13 cases were reported in the literature, and none were reported during 1993–1995 [6]. However, in 1996–1997, more than 500 suspected cases of monkeypox were reported in Kasai-Oriental province, DRC [6, 7]. Only a small number of these cases were laboratory confirmed, and in contrast to the findings of the earlier World Health Organization study, the percentage of secondary cases was much higher (78%) and the fatality rate much lower (1%–5%), suggesting that the great majority were actually cases of varicella. No reports of new suspected monkeypox cases were published until 2001, when 31 patients with monkeypox in 7 separate disease clusters were described in Equateur province, DRC.

Despite political instability and the consequent lack of resources, local health care workers in the DRC continue to perform passive disease surveillance. Their reports indicate that human monkeypox is occurring more frequently than the few published articles would suggest [8] (Program for Control of Monkeypox and Viral Hemorrhagic Fevers, Ministry of Health, Democratic Republic of Congo, unpublished data). Between 1 January 1998 and 31 December 2002, a total of 1265 cases were reported to the DRC Ministry of Health, with specimens collected in 215 cases. Of these 215 cases, PCR and virus culture revealed that 88 were due to MPXV. Of the laboratory-confirmed cases, patient age ranged from 10 months to 38 years, with a mean age of 16.5 years and a median age of 15.5 years. Twenty-six percent of patients were <10 years of age, and 73.2% were <25 years of age [8]. An active disease surveillance system is currently being established in Kasai-Oriental province, DRC, which promises to provide more-extensive and reliable data on the disease.

**US monkeypox outbreak.** In the summer of 2003, MPXV was identified to be the cause of a cluster of cases of disease in the US Midwest [9]. This represented the first occurrence of MPXV in the Western Hemisphere. Of 72 reported cases, 37 human cases were laboratory confirmed during an outbreak [10–12]. Native prairie dogs (*Cynomys* species) housed with rodents imported from Ghana in western Africa were thought to be the primary source of outbreak, because most of the infected people became sick after contact with pet prairie dogs [11]. Although viral transmission appeared to be by direct contact with an infected prairie dog, 2 of the patients provided direct care to their infected children, and the possibility of person-to-person transmission could not be ruled out [9]. Interestingly, in a recent study of 81 health care workers who were exposed to 3 patients with confirmed monkeypox, none reported any signs or symptoms consistent with monkeypox; however, 1 asymptomatic health care worker showed laboratory evidence of recent orthopoxvirus infection, which was possibly attributable to either recent infection or smallpox vaccination [13]. Unlike African patients, most patients from the US outbreak had a mild, self-limited febrile rash illness. Of 69 patients for whom data were available, 18 were hospitalized, although some were hospitalized for isolation precautions only [12]. Two patients, both children, had serious clinical illness [12, 14, 15]. The first child developed severe encephalitis and required intensive care unit hospitalization for 14 days [11, 14]. Encephalitis is a very rare complication of monkeypox, having only been described once previously [4, 16]. The second child was hospitalized with profound painful cervical and tonsillar lymphadenopathy and diffuse pox lesions, including lesions throughout the oropharynx [15]. Both children ultimately recovered, and there were no deaths associated with the outbreak. Interestingly, only 1 patient (a child) had a generalized rash similar to that seen in previous African patients, although many patients developed only localized lesions on the hands and fingers associated with direct contact with infected animals (figure 1). This might be because inoculation of a strain of MPXV via prairie dog bites causes illness that is much milder than that associated with inhalation of the same strain, which is also less virulent than Congo basin isolates [17].

**HUMAN MONKEYPOX**

Monkeypox was first reported as a human disease in a 9-month-old child from Zaire in 1970 [18, 19]. Indeed, until recently,
most clinical data on human monkeypox came from investigations of outbreaks in central and western Africa. It is believed that the virus is transmitted to humans during handling of infected animals or by direct contact with the infected animal’s body fluids or lesions. Person-to-person spread by large respiratory droplets during prolonged face-to-face contact can occur but is much less efficient than that seen with smallpox [20].

The clinical features of human monkeypox closely resemble those of ordinary smallpox [2]. After a 10–14-day incubation period, prodromal illness with fever, malaise, and swollen lymph nodes is observed in most of the patients before the development of rash [4, 21]. Other signs and symptoms of monkeypox include chills and/or sweats, headache, backache, sore throat, cough, and shortness of breath. Lymphadenopathy, which has been observed in 90% of unvaccinated patients, is not a common feature of smallpox and is therefore considered to be a key distinguishing feature of monkeypox (figures 2A and 2B). Lymph node enlargement can occur in the submandibular and the cervical or inguinal regions [20]. The prodromal period generally lasts 1–3 days before the occurrence of the typical maculopapular rash. During the first 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-week period, lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation (figure 2) [20]. Although the rash starts mainly on the trunk, it can spread in a peripheral distribution to the palms and soles of the feet. Lesions can be observed on mucous membranes, in the mouth

Figure 1. A, Vesicle and erythema on the hand of a woman on day 1 of monkeypox virus (MPXV) infection during a US outbreak of monkeypox in 2003. B, Satellite vesicles after biopsy on day 3 after MPXV infection. C, Crusted primary MPXV infection sites on the hands of a woman (on day 9 after infection) and her child. Photographs were kindly provided by Marshfield Clinic, Marshfield, Wisconsin.

Figure 2. A, A 3-year-old African boy with monkeypox and axillary lymph node enlargement (arrow). B, A 7-year-old African girl with monkeypox and bilateral inguinal lymphadenopathy (arrows). For both patients, lymphadenopathy was the main differential diagnostic criterion that distinguished monkeypox from smallpox. Photographs were kindly provided by Mark Szczesniowski, World Health Organization. C, A 7-year-old girl from Tokondo village, Kasai-Oriental province, Democratic Republic of Congo, with reported exposure to a dead monkey. Note the characteristic pustules on her back. Photograph was taken on 4 October 2004 and kindly provided by Dr. Robert Shongo.
Figure 3. Electron micrograph of a human skin biopsy specimen from a monkeypox virus–infected patient. A, Keratinocytes with large numbers of mature virions (solid arrow) and immature virions in the process of assembly (dashed arrow). B, At left, there are 2 cross-sections of mature virus particles that have the characteristic dumbbell-shaped inner cores of poxviruses. At right, the slightly larger round object is an immature virus particle that is not fully assembled. Micrographs were kindly provided by Marshfield Clinic, Marshfield, Wisconsin.

and tongue, and on the genitalia. In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%-5%), and encephalitis (<1%) can be observed in patients infected with MPXV [21]. The fatality rate is 10%, and death generally occurs during the second week of the disease [20, 22].

DIAGNOSIS

Because the clinical picture of monkeypox is very similar to that of chickenpox and that of smallpox, definitive diagnosis is key to keeping natural disease under control or in the early detection of a potential bioterrorism event. The evaluation criteria in the differential diagnosis for patients with monkeypox, chickenpox, or smallpox are shown in table 1. Although diseases such as orf and bovine stomatitis (which are caused by parapoxviruses) can produce localized skin lesions similar to those seen in the US monkeypox outbreak, they can be easily distinguished from orthopoxviruses by electron microscopy. Once the disease agent is identified, quarantine and immediate ring vaccination are the only effective public health protective procedures, because there is no effective, licensed antiviral therapy for monkeypox. Given the ease of transmission through direct contact and aerosol particles, specimens such as scab or other cutaneous tissues should be handled with care and collected aseptically with respiratory precautions.

Although clinical characteristics can be useful in distinguishing poxvirus infections from other causes of vesiculopustular rashes, laboratory confirmation is required for a definitive diagnosis. The various laboratory diagnostic assays for monkeypox include virus isolation and electron microscopy, PCR, IgM and IgG ELISA, immunofluorescent antibody assay, and histopathologic analysis. Unfortunately, many of these methods are relatively nonspecific and are unable to differentiate MPXV infection from infection with other poxviruses. For example, histologically, the lesions of monkeypox are similar to other viral exanthems (such as those due to variola, cowpox, varicella-zoster, and herpes simplex viruses) and include ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation [23]. However, immunohistochemistry analysis, including use of either polyclonal or monoclonal antibodies against all orthopoxviruses, can differentiate between a herpes virus and poxvirus infection. Electron microscopy has often played a major role in viral diagnosis in the past [24]. Likewise, if available, electron microscopy can be a first-line method for laboratory diagnosis of poxvirus infections and may provide one of the first clues to the cause of an unknown rash illness. Characteristic poxvirus virions showing the typical morphology (i.e., brick shape with lateral bodies and a central core) would be expected to be observed under electron microscopy. For example, during the recent US outbreak of monkeypox, lesions viewed by means of electron microscopy showed keratinocytes with large numbers of mature virions, as well as immature virions in the process of assembly (also known as “viral factories”) within the cytoplasm (figure 3) [23]. This method, however, cannot differentiate orthopoxvirus species. Virus isolation (which can be accomplished by growing the virus in mammalian cell culture) and characterization by various PCR techniques, followed by restriction fragment–length polymorphism analysis or sequencing of amplicons, are often considered to be definitive for the identification of MPXV [25]. In addition, the availability of various
Table 1. Evaluation criteria for the differential diagnosis of patients with monkeypox, smallpox, and chickenpox.

<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>Symptom</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>Homogenous rash</td>
<td>Homogenous rash</td>
<td>Heterogeneous 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>
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</table>

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

real-time PCR assays that use panorthopoxvirus or MPXV-specific targets has increased in recent years [26, 27]. A DNA oligonucleotide microarray with the TNF receptor gene crmB has also been developed as another rapid method for species-specific detection of orthopoxviruses [28].

In contrast to regions outside of Africa, where it is essential to distinguish between monkeypox and a deliberate introduction of smallpox, the principal diagnostic problem in sub-Saharan Africa is to differentiate monkeypox from varicella. During active disease, laboratory confirmation can be performed by PCR analysis of vesicle fluid or scabs, whereas after disease resolution, testing of convalescent-phase serum specimens for anti–varicella virus IgM can be performed. The finding of antipoxvirus antibodies in an unvaccinated individual with a history of severe illness and rash suggests a diagnosis of monkeypox.

PREVENTION AND TREATMENT

Vaccination combined with an aggressive surveillance program ultimately resulted in the global eradication of smallpox. Unfortunately, eradication of monkeypox is not possible because of the existence of an animal reservoir. However, vaccination with vaccinia virus (the smallpox vaccine) is highly protective against infection with MPXV [4, 29–31]. In fact, researchers in the 1960s showed that monkeys could be successfully immunized against monkeypox by smallpox vaccination [32]. In addition, not only were reduced numbers of human monkeypox cases observed in Africa among persons who were vaccinated, many of the cases were extremely mild (with very few lesions), and some cases may have been subclinical [20, 30]. For these reasons, the Centers for Disease Control and Prevention recommends pre-exposure vaccination for persons who are investigating animal or human monkeypox cases, health care workers who are caring for patients with monkeypox, anyone who has direct contact with suspected MPXV-infected animals, and laboratory workers who handle specimens that may contain MPXV [33]. In terms of postexposure treatment, vaccination within 4 days after initial close contact with a confirmed monkeypox case is recommended by the Centers for Disease Control and Prevention; however, vaccination should be considered up to 14 days after exposure [33]. Although vaccinia immune globulin is currently recommended for treating severe generalized vaccinia, eczema vaccinatum, and progressive vaccinia [34–36], no data are currently available on its effectiveness for treating human monkeypox. It is unknown whether a person with severe MPXV infection will benefit from treatment with immune globulin. However, such therapy may be considered as a prophylactic for use in an exposed person with severe immunodeficiency in T cell function for whom smallpox vaccination would be contraindicated [33].

There are currently no licensed antiviral drugs available for the treatment of MPXV infection. In the 1950s, a number of thiosemicarbazone derivatives were found to inhibit the replication of vaccinia virus. Specifically, methisazone (Marboran; Burroughs Wellcome) became the first antiviral drug to be introduced into clinical use, but it was fairly toxic when administered systemically and is no longer in use [34]. Cidofovir is a broad-spectrum antiviral drug that has activity against many DNA viruses, including MPXV [37], and is licensed under the name Vistide (Gilead) for treating cytomegalovirus retinitis in patients with AIDS. Cidofovir has not been used to treat orthopoxvirus infection in humans but has been tested extensively in laboratory animals [38–42]. The risk of drug therapy must be examined and weighed against the severity of poxvirus disease, because cidofovir must be administered intravenously and accompanied by probenecid and hydration to avoid renal toxicity. Modified forms of cidofovir that can be given orally are currently in development and have shown some promise in a
mouse model of orthopoxvirus infection [43]. Several other compounds have shown antipoxvirus activity in vitro or in various small animal models [44, 45], but much work needs to be performed, especially in nonhuman primates, before a licensed drug will be available to treat human monkeypox infections.

CONCLUSION

Monkeypox occurs mainly in the jungles of central and western Africa. The disease, unlike smallpox, is a typical zoonosis in that most cases occur as a result of direct contact with an infected animal. The symptoms of the disease in humans can be very similar to those of smallpox, chickenpox, or other causes of vesiculopustular rash; therefore, accurate and rapid laboratory diagnostics are paramount in controlling an outbreak. The similarity of African monkeypox cases to smallpox cases, as well as the growing lack of immunity in the population since the discontinuation of routine smallpox vaccination, has led to the concern that MPXV might be used as a bioweapon. For these reasons, MPXV, along with variola virus and other poxviruses, has been placed on the National Institutes of Health’s highest category threat list (National Institute of Allergy and Infectious Diseases Category A priority pathogen) and is considered to be a “select agent” (defined as bacteria, viruses, toxins, rickettsia, and fungi that pose a potential threat to public health or welfare) by the Centers for Disease Control and Prevention. Although not a result of bioterrorism, the introduction of a disease such as monkeypox into a new, previously disease-free region of the world, as happened with the 2003 monkeypox outbreak in the United States, can cause substantial alarm and even fear. This event has brought attention to the issues related to trade of exotic pets and has further raised concerns pertaining to the increasing global transport of wild animals and other potential vectors of infectious diseases once thought to be geographically restricted and not a concern for the United States. In November 2003, the Centers for Disease Control and Prevention and the Food and Drug Administration issued the interim final rule to prohibit the import, capture, transport, sale, barter, exchange, distribution, and release of African rodents, prairie dogs, and certain other animals into the environment, to prevent the spread of monkeypox in the United States.

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