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Monkeypox Virus Infections

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Introduction

Monkeypox is an uncommon viral zoonosis caused by a member of the genus Orthopoxvirus (Breman, 2000). The disease is important to public health because the monkeypox virus (MPV) has a close genetic relationship to another orthopoxvirus, variola virus (smallpox virus), and is capable of causing a clinical syndrome that resembles that caused by variola virus. Other important orthopoxviruses causing infections in humans include vaccinia virus (used for smallpox vaccination) and cowpox virus.

MPV was named as such because it was first recognized in association with nine outbreaks of vesicular exanthems among captive primates in laboratories and zoos during the 1950s and 1960s (Arita and Henderson, 1968; Arita et al., 1972). The first cases of human disease caused by this virus were reported in 1970 in Zaire (now the Democratic Republic of Congo). Prior cases of human monkeypox undoubtedly occurred in central Africa but most likely were confused with smallpox. Since its initial recognition, monkeypox has been documented to occur sporadically in humans throughout central and western Africa, and is considered by some to be the most important orthopoxvirus now that smallpox has been eradicated.

Renewed interest in human monkeypox was generated by the unexpected emergence of the disease in the midwestern U.S. associated with the importation of infected rodents from western Africa (Reed et al., 2004). Additional interest has focused on MPV because it is considered to be a potential agent of bioterrorism.

Description of the agent

MPV is a large, complex, double-stranded DNA virus of the chordopoxvirus family. MPV is endemic in central and western Africa and is a classic zoonosis acquired
through contact with infected rodents and squirrels. Secondary spread from person to person can occur among close contacts, but this occurs much less frequently than with smallpox virus. Two genetic clades of MPV are recognized, a Congo basin-derived clade associated with 2–10% mortality in unvaccinated individuals, and a west African clade associated with milder illness and very low mortality (Chen et al., 2005; Likos et al., 2005).

Epidemiology of MPV infections

Human monkeypox has probably occurred in central and western Africa for hundreds, if not thousands, of years but was overshadowed by smallpox until variola virus was eradicated in central Africa in the late 1960s. Unlike variola virus, MPV is a zoonotic pathogen. However, there is surprisingly little detailed information on the enzootic cycle of MPV in nature. Humans and monkeys are generally considered incidental hosts and the reservoirs that amplify the virus in natural settings are probably rodents or squirrels that inhabit the sub-Saharan rain forests (Khodakevich et al., 1988). Laboratory studies indicate MPV has a broad host range and can infect numerous species of small mammals. Field studies from the Democratic Republic of Congo have shown that rope squirrels and tree squirrels (Funisciurus and Heliosciurus spp., respectively) and Gambian giant rats (Cricetomys spp.) that inhabit agricultural areas have high seroprevalence rates for MPV and seem to be important in sustaining viral transmission in agricultural areas (Khodakevich et al., 1986).

Epidemiologic studies during 1970–1979 documented 47 cases of human monkeypox worldwide. Most of these cases \((n = 38)\) occurred in the Democratic Republic of Congo with the remainder in the western African countries of Gabon, the Ivory Coast, Liberia, Nigeria, and Sierra Leone. Cases in the Democratic Republic of Congo were highly associated with animal contact and seven of the 47 cases \((14.9\%)\) were fatal. Secondary transmission occurred among 7.5% of family members (Breman et al., 1980).

Over the years there has been great concern that monkeypox might have the potential to emerge from central Africa and replace smallpox as a global health problem, but this appears to be unlikely. World Health Organization (WHO) surveillance between 1981 and 1986 in the Democratic Republic of Congo revealed that \(> 70\%\) of cases were associated with an animal source of infection; the remainder were due to secondary transmission. Most cases occurred in children and the mean age was 4.4 years. Although the rate of secondary transmission was several times higher than that observed during the 1970s, in no instance did the chain of transmission go beyond four generations, suggesting that MPV has low potential for epidemic spread (Jezek et al., 1986; Jezek and Fenner, 1988). Stochastic modeling of MPV transmission supported that conclusion (Jezek et al., 1987a). More recently, extended person-to-person transmission of MPV was observed in a hospital in the Democratic Republic of Congo where up to six sequential transmission cycles were hypothesized to have occurred (Learned et al.,
This pattern of sustained transmission suggests that MPV may have the capacity to adapt to the human host more than that been previously observed.

The number of reported cases of human monkeypox declined after formal WHO surveillance ended in 1986. From 1986 to 1992, only 13 cases were reported in the medical literature and none were reported from 1993 to 1995 (Heymann et al., 1998). This trend suddenly reversed in 1996–1997 when more than 500 cases of suspected monkeypox were reported in the Kasai-Oriental province of Democratic Republic of Congo. This outbreak was associated with a low fatality rate (1–5%) and high person-to-person transmission (78%) compared to previous outbreaks. Since many of these suspected cases were not laboratory confirmed, some authors have speculated that the majority of cases were actually due to varicella rather than MPV (Hutin et al., 2001). From 1998 to 2002, greater than 1200 cases of monkeypox were reported to the Democratic Republic of Congo Ministry of Health. Of those cases that were laboratory confirmed, patient’s age ranged from 10 months to 38 years (mean of 16.5 years) (Kebela, 2004). Active and passive surveillance for monkeypox continues on the African continent but is hampered by political unrest and lack of adequate public health resources.

In May and June of 2003, human MPV infections were identified for the first time in the western hemisphere (Reed et al., 2004). In total, 72 cases were reported, with 37 confirmed by laboratory testing. Epidemiologic investigation indicated that nearly all of the patients had been exposed directly or indirectly to ill prairie dogs (Cynomys spp.) that had been kept or sold as pets. Two of the patients were parents of other patients, who had provided direct care to their infected children and could possibly have acquired MPV by person-to-person transmission.

The prairie dogs had been housed with rodents that were part of a large shipment of animals imported from Ghana in western Africa. The shipment included rope squirrels, tree squirrels, Gambian giant rats, brushtail porcupines (Atheurus spp.), dormice (Graphiurus spp.), and striped mice (Hybomys spp.). Laboratory testing revealed that at least one Gambian giant rat, two rope squirrels, and three dormice were infected with MPV. Some of the infected rodents were sold to a pet distributor in the Chicago area, to which they were transported in association with prairie dogs. The exposed (and infected) prairie dogs were then sold to the index patient and others at pet “swap meets” in Wisconsin, Illinois, Indiana, and Ohio. Cases were also reported in Kansas and Missouri (MMWR, 2003).

Most of the patients in the U.S. outbreak had mild, self-limited disease in comparison to the more severe illness reported among African patients. The milder illness can be explained in part by the fact that many of the adults who were infected had previously received smallpox vaccination. In addition, the strain of MPV associated with the U.S. outbreak was of west African origin and is known to be less virulent than the Congo basin-derived strains. Of 69 patients for whom data are available, 18 were hospitalized. No deaths were reported. Two pediatric patients had serious clinical illness; one child had severe encephalitis requiring treatment in an intensive care unit for 14 days and the other had diffuse pox lesions and
painful cervical and tonsillar lymphadenopathy and oropharyngeal lesions (Anderson et al., 2003; Huhn et al., 2005).

A significant concern during the outbreak in the U.S. was the possibility that MPV infection could spread to North American rodent populations and establish a zoonotic sylvan cycle of infection. To date, extensive investigations of that possibility have provided no evidence that MPV extended into local rodent populations as a result of the 2003 outbreak in humans and prairie dogs sold as pets.

Clinical features

The first human MPV infection was recognized in 1970 in a 9-month-old child living in Zaire, not long after smallpox was considered to have been eradicated from that country (Ladnyj et al., 1972). Over the next decade, clinical manifestations of MPV infection remained poorly defined, because fewer than 50 cases were documented. Initial descriptions suggested that the disease resembled smallpox in terms of morbidity and mortality, but that it was distinct in having low transmissibility between humans (Breman et al., 1980).

Observational studies of human monkeypox in central and western Africa during the 1980s revealed that MPV infection had an incubation period of 10–14 days and a period of infectivity during the first week of rash. MPV enters the body through skin abrasions, the upper respiratory tract mucosa, or by ingestion. During primary viremia the virus migrates to regional lymph nodes and then disseminates throughout the body. A prodrome of fever and malaise typically occurs 1–2 days prior to the onset of a rash and is associated with lymphadenopathy in around 90% of cases. The distribution of lymphadenopathy is variable and can include submandibular, cervical, axillary, and inguinal areas. It is important to note that smallpox is rarely associated with significant lymphadenopathy, making this a key distinguishing clinical feature between the two diseases.

The rash caused by MPV begins as papular lesions of 1–5 mm in diameter that progress through vesicular, pustular, and crusted stages over a period of 14–21 days (Fig. 1). The crusts eventually slough off, leaving depressed scars. Case descriptions from Africa emphasize a centrifugal pattern of spread that becomes generalized over time. However, a centripetal distribution of the rash, similar to that seen in chickenpox, has been described in a few cases (Jezek et al., 1987b).

Several unique clinical manifestations were noted among patients infected during the 2003 outbreak of monkeypox in the U.S. These included focal hemorrhagic necrosis, particularly at the sites of bites or scratches, and erythematous flares that may have been more apparent on light skin (Reed et al., 2004). The list of differential diagnoses for the rash lesions of monkeypox is long and includes smallpox, chickenpox, orf another name for contagious ecthyma. It is a parapoxvirus infection of sheep and goats that is transmissible to man, milker’s nodule, erythema multiforme, drug eruptions, rickettsialpox, and eczema herpeticum.

Extracutaneous manifestations of MPV infection include cough, pharyngitis, a feeling of chest tightness, nausea, diarrhea, myalgia, and back pain. Complications
Inoculation lesions

Dissemination lesions

Evolution of primary lesions

Fig. 1 Cutaneous lesions of human monkeypox. The top panels show primary inoculation lesions at the site of a prairie dog bite (A) or scratch (B and C). The middle panels show the variation of the appearance of disseminated lesions of monkeypox ranging from smallpox-like (D) to varicella-like (E–J). The lower panels (K–M) document the progression of a primary lesion from the pustular stage through scarring. (For colour version: see Colour Section on page 351).
can include secondary infections of skin and soft tissue (20%), pneumonitis (12%), ocular involvement (5%), and rarely, encephalitis (<1%) (Nalca et al., 2005).

Prior smallpox vaccination modulates the clinical course of human monkeypox disease in a number of aspects. In general, patients who were previously vaccinated against smallpox experience a milder illness and have lower morbidity and mortality. The rash of MPV infection tends to be more pleomorphic in individuals vaccinated against smallpox and more closely resembles the rash of chickenpox.

**Laboratory diagnosis**

Human monkeypox is a reportable disease; state and local health departments should be notified immediately of any suspected cases. Although the history and clinical characteristics can be helpful in differentiating between monkeypox and other causes of vesiculopustular eruptions, it is highly desirable that all cases be confirmed by laboratory testing. During the 2003 U.S. outbreak, the Centers for Disease Control and Prevention (CDC) recommended the following laboratory criteria for diagnosing human monkeypox cases: (1) isolation of MPV in culture; (2) demonstration of MPV DNA by PCR testing in a clinical sample; (3) electron microscopic evidence of an orthopoxvirus in the absence of exposure to another orthopoxvirus; and (4) immunohistochemical evidence of an orthopoxvirus in tissue in the absence of exposure to another orthopoxvirus.

MPV grows well in established cell lines and embryonated chicken eggs. Cell lines that MPV grows in include rhesus-monkey kidney, rabbit kidney, MRC-5, RD, B-SC-40, and Vero cells. Cytopathic effect usually occurs within 1–4 days and includes plaques of elongated and rounded cells with prominent cytoplasmic bridging and formation of syncytium. When MPV is grown in embryonated chicken eggs, it produces small, opaque, hemorrhagic pocks on the chorioallantoic membranes of the chicken egg that are distinct from lesions produced by other orthopoxviruses.

Samples from suspected cases of MPV infection that are appropriate for virus isolation include biopsies and touch preparations refer to pressing a glass slide against the lesion so that adherent cellular material can be stained and viewed under a microscope of skin lesions, lymph nodes, oropharyngeal swabs, and whole blood during the prodromal stage (Damon and Esposito, 2003). MPV-infected clinical samples can be handled safely by laboratory personnel who have received smallpox vaccination within the past 10 years and who use strict biosafety level 2 containment. As a practical consideration, most diagnostic laboratories in the U.S. have limited experience with isolating orthopoxviruses from clinical specimens and should refer specimens from suspected cases to their state health laboratory or to the CDC.

A number of molecular diagnostic tests are available to aid in the definitive diagnosis of MPV infections. DNA-based tests, such as PCR with restriction endonuclease digestion or sequencing of the hemagglutinin gene (HA), can confirm the identity of an orthopoxvirus to the species level and can be accomplished in just
a few hours. This method is based on the use of primers EACP1 and EACP2 (for Old World orthopoxviruses) or NACP1 and NACP2 (for New World orthopoxviruses) (Damon and Esposito, 2003). Additional PCR protocols target the A-type inclusion body protein or B cytokine response modifier (Ropp et al., 1995; Meyer et al., 1997; Meyer et al., 1998).

Electron microscopy (EM) is an important front-line method for the laboratory diagnosis of poxvirus infections because it is a simple technique that can rapidly exclude varicella virus (chickenpox), a herpesvirus, from the differential diagnosis (Hazelton and Gelderblom, 2003; Curry et al., 2006). Transmission EM of tissue biopsies reveals virions with dumbbell-shaped inner cores highly characteristic of poxviruses. However, this technique does not distinguish between orthopoxviruses and the other genera of poxviruses. When vesicle fluid or tissue culture supernatants are examined by EM of specimens negatively stained with phosphotungstic acid or another heavy metal, orthopoxviruses have a distinctive brick-shaped appearance with regularly spaced threadlike ridges on the exposed surfaces. In contrast, parapoxviruses appear ovoid with spiraling criss-cross surface projections. Negative stain EM of cell culture supernatants provided the first clues that the 2003 U.S. outbreak was due to an orthopoxvirus (Reed et al., 2004).

The histopathology of monkeypox skin lesions mirrors the clinical progression of these lesions. Early lesions contain ballooning degeneration of basal keratinocytes and spongiosis of a mildly acanthotic epidermis. These progress to full thickness necrosis of a markedly acanthotic epidermis containing few viable keratinocytes. A mixed inflammatory infiltrate and progressive exocytosis with the keratinocyte necrosis appear, involving the superficial and deep vascular plexes, eccrine units, and follicles. Multinucleated syncytial keratinocytes and hyaline intracytoplasmic inclusions appear, reflecting the presence of virus in the cells. The histologic differential diagnosis includes herpes simplex, varicella, and other poxviruses. EM can be used to distinguish between herpesvirus and poxvirus infections. Immunohistochemistry with anti-orthopoxvirus antibodies can be useful to detect viral antigen within the keratinocytes of lesions in the epidermis, in the follicular and eccrine epithelium, and in scattered dermal macrophages (Bayer-Garner, 2005). The histologic, ultrastructural, and immunohistochemical appearance of MPV infection are shown in Fig. 2.

Use of serologic tests to identify MPV infection is difficult because of the close antigenic relationships among the various orthopoxviruses. Neutralization tests, hemagglutination inhibition assays, and ELISAs are available to detect orthopox antibodies in patients’ sera, but the sensitivity of these assays ranges from 50% to 95%. Currently, there is no widely available serologic test that is sensitive and specific for identifying MPV infections (Damon and Esposito, 2003). However, serological testing has proven useful in epidemiologic studies. A retrospective study of individuals potentially exposed to MPV in the 2003 U.S. outbreak revealed three cases of asymptomatic infection that occurred in persons who had been vaccinated against smallpox decades earlier (Hammarlund et al., 2005).
Prevention of MPV infections

Vaccination with vaccinia virus (smallpox vaccine) is highly protective (around 85%) against MPV infection. Post-exposure smallpox vaccination is indicated for persons who are at high risk of MPV infection, including those investigating animal or human monkeypox cases, health care workers caring for infected patients, and laboratory workers who handle specimens that may contain MPV. Vaccination within 4 days after initial close contact with a confirmed monkeypox case is recommended by CDC and should be considered up to 14 days after exposure. Vaccinia immune globulin may be considered as a prophylactic for exposed persons with impaired T-cell function who would not be candidates for vaccination (Di Giulio and Eckburg, 2004).

Treatment of MPV infections

Treatment of severe illness with vaccinia immune globulin should be considered but no data are available documenting sensitivity in treating human monkeypox. There are no antiviral drugs approved for treating monkeypox. Cidofovir is a broad-spectrum antiviral drug with known in vitro activity against cytomegalovirus and many other DNA viruses, including MPV. Although clinical experience with the use of cidofovir in human monkeypox infections is limited, antiviral treatment with that agent was more effective than post-exposure smallpox vaccination in the cynomolgus monkey (Macaca fascicularis) model (Stittelaar et al., 2006).

Transmission of MPV within hospitals has been described but the overall risk appears low. CDC recommends a combination of precautions, including standard, contact, and large droplet precautions for infection control purposes. Airborne precautions for small aerosolized droplets (\(<5\)μm in size) should be implemented whenever possible. All laboratory specimens should be handled in a biological safety cabinet (Fleischauer et al., 2005).

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Fig. 2 Histological, ultrastructural, and immunohistochemical appearance of MPV infection. Panel A: Scattered degenerating and necrotic keratinocytes are shown within the epidermis along with a moderate inflammatory cell infiltrate in the superficial dermis (hematoxylin and eosin). Panel B: Higher magnification of the boxed area shows multinucleated cells (long arrow) and eosinophilic viral inclusion bodies. Panel C: Strong immunoreactivity for orthopoxvirus antigen is present in the epidermis. Panel D: Transmission electron microscopy shows virions within the cytoplasm of a keratinocyte, including immature forms undergoing assembly (long arrow) and mature forms (short arrow). Panel E: High magnification shows the characteristic dumbbell-shaped inner core of poxviruses. Panel F: Negative staining of a virion from cell culture shows the brick-shaped particle with regularly spaced, threadlike ridges on the exposed surface. (For colour version: see Colour Section on page 352).
Conclusions

The 2003 U.S. outbreak of MPV was a sobering reminder of the impact that emerging infectious diseases can have on the public health. That emergence of monkeypox in North America was linked directly to the importation of rodents from West Africa and subsequent co-mingling of these animals with animals native to North America. On June 11, 2003, the CDC and the Food and Drug Administration issued a joint order prohibiting the importation of all African rodents into the U.S. The order also banned within the U.S. any sale, distribution, transport, or release into the environment of prairie dogs and six specific genera of African rodents. On November 4, 2003 the joint order was replaced by an interim final rule that maintained the importation ban. Animals can still be imported for scientific, exhibition, or educational purposes with a valid permit issued by CDC.

Although the close genetic relationship between MPV and smallpox has raised concern about potential for use of MPV as an agent of bioterrorism, the low secondary attack rate and generally self-limited illness associated with MPV in humans makes its use as a weapon unlikely. This situation could change dramatically if genetic engineering were used to increase the transmissibility and virulence of the pathogen to humans, a change that remains only theoretical at present.

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