Camelpox Virus

7

Bidhan Chandra Bera, Thachamvally Riyesh, Sanjay Barua, and Raj Kumar Singh

Abstract

Camelpox is a highly contagious skin disease of camelids caused by camelpox virus (CMLV), a member of genus *Orthopoxvirus* within the family *Poxviridae*. The disease is often manifested as a mild local skin infection and sometimes in the severe form with systemic involvement. The disease is enzootic in the camel-rearing areas of arid and semiarid regions of the world and causes economic loss in terms of morbidity, mortality, loss of weight, and reduction in milk and wool production. The CMLV infection is transmitted mostly by direct contact and aerosol route. The disease gained attention globally in the recent past due to its close similarity with the causative agent of smallpox (variola virus) and irrefutable incidences of few zoonotic infections in humans. Like many other poxviruses, the CMLV has a large DNA genome, capable of encoding genes responsible for replication, host range, immunomodulation, virulence, and other functions. Despite the presence of a myriad of host range genes, the host tropism of camelpox virus is very limited. Both live attenuated and inactivated vaccines are available to combat the disease in camels; however, no vaccine has been developed till date for use in humans. Few antiviral agents have been shown to be effective against CMLV; however, their use is very limited in field outbreaks. The research on CMLV is gaining global interest due to CMLV zoonosis especially in the context of naive human population to poxvirus immunity. The present chapter enlightens the brief overview of background, history, incidence, and prevalence of the disease, immunobiology, diagnostics, risk factors, transmission, and prevention and control of camelpox.

B. C. Bera · T. Riyesh · S. Barua
National Centre for Veterinary Type Cultures, ICAR-National Research Centre on Equine, Hisar, Haryana, India

R. K. Singh (✉)
ICAR-Indian Veterinary Research Institute (ICAR-IVRI), Izatnagar, Uttar Pradesh, India

7.1   Prologue

Camelpox is a highly contagious viral skin disease of camelids, which occurs throughout the camel-rearing areas of the world. The disease mainly occurs in Old World camelids (*Camelus dromedarius and C. bactrianus*) of Africa, the Middle East, and Asia, except dromedary camel in Australia and tylopoda (llama and related species) in South America. The disease affects all animals irrespective of age, breed, and sex; however, young camels (2–3 years old) are found to be more susceptible to the infection. Clinical lesions are confined to the skin with rare systemic infections. The disease is characterized by fever, enlarged lymph nodes, and papular pustular eruptions on the skin. In the systemic form, pock lesions are found in the mucous membranes of the mouth and respiratory and digestive tracts. The disease causes a considerable economic impact in terms of morbidity, mortality, loss of weight, and reduction in milk, meat, and wool production. The disease also results in the imposition of trade restrictions on camels and their by-products. The morbidity rate is variable depending on the circulating viral strains. The mortality rate in adult animals is between 10% (Higgins et al. 1992) and 28% (Jezek et al. 1983) and in young animals between 25% and 100% (Mayer and Czerny 1990). The infection generally occurs by direct contact between infected and susceptible animals or indirectly via a contaminated environment through inhalation or skin abrasions.

The etiology of the disease is camelpox virus (CMLV), a member of the genus *Orthopoxvirus* (OPV) and the subfamily *Chordopoxvirinae* in the family *Poxviridae*. Other important members of the genus (i.e., *Orthopoxvirus*) include human pathogens such as variola (smallpox), monkeypox, cowpox, and vaccinia viruses (Moss 2013). The CMLV is similar to the prototypic VACV with respect to size, shape, structure, physicochemical properties, and replication mechanisms. Like other OPVs, CMLVs are large, and average virion size is $217.6 \pm 18.7 \times 293.15 \pm 18.8$ nm (Erster et al. 2018). CMLV is secreted in milk, saliva, and ocular and nasal discharges, and the virus can survive in dried scabs for at least 4 months. The genome of CMLV consists of a linear double-stranded DNA with hairpin loops at the terminal portion (Moss 2007). The full-length genome sequences of three CMLV strains CMLV-CMS, CMLV-M96, and 0408151v have been unveiled, and the genome size has been found to range from 202 to 205.7kbp (Afonso et al. 2002; Gubser and Smith 2002). The detailed analysis of genome sequence and phylogeny has revealed the close relationship of CMLV with the variola virus (VARV), the causative agent of dreadful "smallpox" disease, which had been eradicated in 1980 (Afonso et al. 2002; Gubser and Smith 2002). The in vitro growth characteristics in respect to pock formation on chorioallantoic membrane (CAM), growth in cells, and low or absence of pathogenicity in various animal models also reiterate that CMLV has strong similarities to VARV (Baxby 1972, 1974; Baxby et al. 1975). More focused

studies on genomic, biological features and pathogenesis of CMLV are getting the impetus for better understanding of the biology of VARV.

CMLV is highly host-specific and does not infect other animal species. However, jumping of CMLV in spillover hosts like human and causing infections have been documented in literature. Earlier reports had described mild skin lesions in humans associated with camelpox virus infections (Jezek et al. 1983; Lesse 1909). Recently, the conclusive reports of CMLV zoonosis have been reported from India (Bera et al. 2011) and Sudan (Khalafalla and Abdelazim 2017). The human infections with CMLV have been confirmed on the basis of clinical and epidemiological features coupled with serological tests and molecular characterization of the causative agent. Hence, CMLV can act as an occupational public health hazard. The emergence of CMLV zoonosis certainly points toward a declining immunity against OPVs in humans, which could be of serious public health concern. Due to the frequent outbreaks of CMLV and other poxvirus diseases in animals and their transmission to spillover hosts including humans, focused attention is required on understanding the ecology and epidemiology of the disease, the identification of potential reservoirs of these poxviruses, the transmission chain, and the immune response upon natural infection, improved diagnostics, and new-generation vaccines in order to control the disease in camels and zoonotic infection in the near future.

7.2   History

Poxviruses are the best known and most feared viruses of humans and animals. Viruses of the family *Poxviridae* are very large in size (220–450 nm × 140–260 nm) and have a double-stranded DNA genome of size ranging from 130 to 375 kbp. Only members of the subfamily *Chordopoxvirinae* are capable of infecting vertebrate species. As per the latest ICTV classification (2017), the subfamily contains 13 genera (including two unassigned genera), of which genera *Orthopoxvirus* (OPV), *Parapoxvirus*, and *Yatapoxvirus* contain viruses with zoonotic potential and gained much attention recently. The most prominent species of the genus *Orthopoxvirus* (OPV) is variola virus (VARV), the causative agent of smallpox, which was a threat for humans worldwide for centuries. In addition to VARV, the genus OPV also contains many other viruses with or without zoonotic potential (Table 7.1). The infection caused by other OPVs didn't get much attention till the eradication of smallpox, because smallpox was the most dreaded viruses among all these members. Eradication of human smallpox in the late 1970 and subsequent cessation of small vaccination resulted in a human population with waning antibodies against poxviruses. This resulted in an increased incidence of human cases of cowpox virus in Europe, monkeypox in Africa, and bovine vaccinia virus infection in India and Brazil. Since then, the knowledge on poxviruses is increasing at an incredible speed, and many poxvirus diseases are getting much attention among researchers and public health authorities.

Camelpox is one such disease, which got major attention in the early 1970s although the outbreak was reported a long time back, for the first time, from India

Table 7.1 Classification of *Orthopoxvirus* and their host range

Family: *Poxviridae*		
Subfamily: *Chordopoxvirinae*		
Genus	*Species*	Host
Orthopoxvirus	*Camelpox virus*	Camel, human
	Cowpox virus	Cattle, human, cats, dogs, rodents, nonhuman primates, elephant, rhinoceros, gerbils
	Ectromelia virus	Laboratory mice, wild mice, wild rodents
	Monkeypox virus	Monkeys, apes, human, rope squirrel (*Funisciurus anerythrus*), sooty mangabey (*Cercocebus atys*)
	Raccoonpox virus	Raccoons (*Procyon lotor*)
	Skunkpox virus	Skunk (*Mephitis mephitis*)
	Taterapox virus	African gerbil (*Tatera kempi*)
	Vaccinia virus	Human, cattle, buffalo, rodents
	Variola virus	Human
	Volepox virus	Vole (*Microtus californicus*) Pinyon mouse (*Peromyscus truei*)

(Lesse 1909). Since then, the disease has continuously been reported from many countries. For a long period, the disease has been recognized as a generalized pox disease of camels, and the causative virus (CMLV) was first isolated by cultivation in chick embryos in 1970 (Sadykov 1970). Later, CMLV was also isolated in tissue culture in 1972 (Ramyar and Hessami 1972). In the late 1970, CMLV was considered as "smallpox-like" member of the genus *Orthopoxvirus*, due to its similarities with VARV in the form of culture characteristics, narrow host range, and even serological cross-reactivity (Baxby 1972; Baxby et al. 1975; Davies et al. 1975). The speculation of similarities among CMLV and VARV was further supported by findings of in vivo experiment, where camels infected with VARV strain EA8 were protected against challenge with an infective dose of CMLV (Baxby et al. 1975). This raised a great concern among those involved in the global smallpox eradication campaign. However, 20 years later, the genome characterization studies by restriction fragment length polymorphism analysis using *HindIII* enzyme confirmed that CMLV was a separate member of OPV genus (Pfeffer et al. 1996; Renner-Muller et al. 1995). Subsequently, the full-genome sequence of CMLV strains depicted that CMLV is closest to VARV, sharing several genes involved in basic replication and host-related functions, and, probably, they may share a common ancestor (Afonso et al. 2002; Gubser et al. 2007a, b). A recent isolate of CMLV from Israel was found to be genetically different from the currently annotated camelpox isolates; however, complete genome sequencing is essential to arrive at a conclusion (Erster et al. 2018).

7.3   Incidences and Prevalence

Camelpox is prevalent in almost every camel-rearing regions of the world. Since the first report of the disease from India in 1909, regular incidences of CMLV infections have been reported from many countries of the world with large number of recorded outbreak being reported after the year 1972. The disease has been reported from Middle East (Bahrain, Iraq, Iran, Israel, Oman, Saudi Arabia, United Arab Emirates, and Yemen), Asia, (India, Afghanistan, Pakistan, Kazakhstan, and Turkmenistan), Africa (Algeria, Egypt, Ethiopia, Kenya, Mauritania, Morocco, Niger, Somalia, Sudan, and Syria), and southern part of Russia (Wernery and Kaaden 2002; Duraffour et al. 2011; Erster et al. 2018). The incidence of disease outbreaks in different countries/regions has been depicted in Table 7.2. It is interesting to mention that camelpox has never been reported from Australia in spite of the presence of natural populations of dromedary camels and camel farming (Wernery and Kaaden 2002). Similarly, disease has not been described in llama and related species (New World camelids) of South America (Duraffour et al. 2011)).

The overall epidemiological data of camelpox is limited. Camelpox outbreaks are often temporal in nature due to the movement of camels for grazing which results in mixing of the infected camels. Generally, young camels under the age of 4 years and pregnant females are more susceptible to the disease. The mean morbidity rates of the disease can be as high as 100%, while the mean mortality rates may range from 0% to 15%, and the case fatality rates may vary from 0% to 25% (Alhendi et al. 1994; Abu Elzein et al. 1999; Duraffour et al. 2011). The prevalence studies of this disease at Jazon region of Saudi Arabia during the period 2003–2004 revealed that mortality was higher in camels of less than 1 year of age (83%) followed by camels of less than 1–4 and above 4 years of age (8.3% each) (Ommer Dafalla and Abdelhamid Elfadil 2007). Among the endemic Southeast Asian countries (India, Pakistan, and Afghanistan), majority of the outbreaks are reported from India. CMLV outbreaks have regularly been reported from the North Central regions – the primary camel-rearing parts of the country (Chauhan and Kaushik 1987; Khanna et al. 1996; Marodam et al. 2006; Balamurugan et al. 2008, 2009; Bhanuprakash et al. 2010, Bera et al. 2011; Dahiya et al. 2017). Though the disease is endemic in India, sporadic outbreaks occur during the rainy season. Other countries like Ethiopia (Gelaye et al. 2016), Sudan (Khalafalla and Abdelazim 2017), and Israel (Erster et al. 2018) also witnessed camelpox outbreak in recent times.

Although CMLV is highly species-specific in infecting camels, the reports of human infections associated with camelpox have raised a debate on zoonotic nature of the virus. The first case of human camelpox was described in Somalia in a 40-year-old camel herder (Kriz 1982); however, the association of CMLV in the affected individual could not be confirmed (Kriz 1982; Jezek et al. 1983). The first indisputable proof of zoonotic CMLV infections in three human cases associated with camelpox outbreaks (2009) in dromedary camels has been recently reported from India (Bera et al. 2011). Subsequently, another report described the conclusive human case of CMLV infection related to the camelpox outbreaks (2014) in dromedary camels in Sudan (Khalafalla and Abdelazim 2017). The increasing incidences

Table 7.2 Some of the outbreaks of camelpox in different regions of the world

Continent/country/region	Outbreaks reported	Reference
Middle East		
Bahrain	1992	Higgins et al. (1992)
Iran	1972, 2014	Baxby (1972); Mosadeghhesari et al. (2014)
Iraq	1977, 2001, 2007, 2013	Falluji et al. (1979); Gatie (2016)
Saudi Arabia	1986,1994, 1999, 2003, 2004, 2009	Hafez et al. (1992); Alhendi et al. (1994); Abu Elzein et al. (1999); Ommer Dafalla and Abdelhamid Elfadil (2007); Yousif and Al-Naeem (2011)
United Arab Emirates	1995, 1993, 1994	Renner-Muller et al. (1995); Pfeffer et al. (1996)
Israel	2016	Erster et al. (2018)
Asia		
India	1909, 1987, 1996, 2006, 2008, 2009, 2011, 2014, 2016	Lesse (1909); Chauhan and Kaushik (1987); Khanna et al. (1996); Marodam et al. (2006); Balamurugan et al. (2008, 2009); Bhanuprakash et al. (2010); Bera et al. (2011); Dahiya et al. (2017); Narnaware et al. (2018)
Pakistan	1997, 2010	Khan (2010)
Kazakhstan	1978	Tantawi et al. (1978)
Turkmenistan	1978	Tantawi et al. (1978)
Africa		
Egypt	1974, 2009	Tantawi et al. (1974); Mahmoud et al. (2012)
Ethiopia	2001, 2011, 2012, 2013, 2014	Tefera and Gebreah (2001); Ayelet et al. (2013); Gelaye et al. (2016)
Kenya	1975, 1992	Davies et al. (1975); Gitao (1997)
Libya	1996	Azwai et al. (1996)
Mauritania	1989	Nguyen-Ba et al. (1989)
Morocco	2000	El-Harrak and Loutfi (2000)
Niger	1989	Nguyen-Ba et al. (1989)
Somalia	1982	Kriz (1982)
Syria	2005	Al-Zi'abi et al. (2007)
Sudan	1992, 1994, 1998, 2013, 2014	Khalafalla et al. (1998); Khalafalla and Mohamed (1998); Motalab and Ahmed (2014); Khalafalla and Abdelazim (2017)

of human CMLV infections raise the concern of camelpox zoonosis and public health safety especially in the context of reduction of cohort immunity in human population against OPVs after the cessation of smallpox vaccination. Further, antibody prevalence rates of 6% and 10% have been observed in sheep and goat, respectively, in Saudi Arabia, suggesting potential adaptation of camelpox in hosts other than camel in enzootic areas (Housawi 2007; Duraffour et al. 2011).

7.4   Immunobiology

The immune response to CMLV is mediated through both humoral and cell-mediated immune arms of the immune system. At early stage of infection, the host innate immune response tries to prevent the infection, while the acquired immune response is mounted. Various host defense components like complement, interferon, NK, and inflammatory cells play an important role to control the early infection. However, within a few days of infection, the poxvirus-specific antibodies are generated to control the infection. Simultaneously, a cell-mediated immune response is also generated through the production of poxvirus-specific cytotoxic T cells (CTLs), which kill the virus-infected cells resulting in the clearance of the poxvirus infection. Like many other *Orthopoxvirus*, CMLV infections also produce long-lasting immunity in recovered animals. For successful transmission and multiplication in host cells, viruses require the ability to evade or subvert the innate and acquired host immune responses. Poxviruses encode multiple classes of immunomodulatory genes capable of inhibiting diverse immune mechanism of host cells such as apoptosis, complement activation, activity of natural killer (NK) cells and CTLs, and production of interferons and inflammatory cytokines. Immune-modulation mechanisms of VACV and CPXV have been well described, but reports on immune-modulation mechanisms of CMLV are limited. However, complete genome sequencing of CMLV has brought additional knowledge on immunomodulatory proteins encoded in its genome. The functions of some of these proteins have been studied experimentally. The ORF CMLV-CMS-007 encodes a virus Golgi antiapoptotic protein (v-GAAP), which inhibits apoptosis (Gubser et al. 2007a). CMLV also expresses novel virulence factor, the Schlafen-like encoded by ORF CMLV-CMS-226 affecting the host immune response to infection (Gubser et al. 2007a, b). The gene 252 of CMLV-CMS encodes a protein capable of binding to IFN-α and blocks its activity (Alcami et al. 2000; Montanuy et al. 2011; Symons et al. 1995). The ORF CMLV-CMS-233 encodes an IFN-γ receptor which binds to host IFN-γ and prevents its interaction with cellular receptor (Alcami and Smith 2002). The ORFs CMLV-CMS-002 and 265 encode soluble virus tumor necrosis factor receptor II CrmB (vTNFR); however, its action has not been studied in detail (Alcami et al. 1999). The virus chemokine-binding protein (vCKBP) encoded by CMLV-CMS-001 and 266 has been found to bind with CC chemokines and affect their interaction with cellular receptors (Alcami et al. 1998). In addition, CMLV also contains genes which have high sequence similarity with immunomodulatory genes present in other poxvirus, hence assumed to have a similar biological activity/function. The products of gene CMLV-CMS-115 have been shown to prevent the action of IFN-γ on infected cells. The products of ORF CMLV-CMS-115 has been shown to prevent activation of PKR (dsRNA-dependent protein kinase), thereby decreasing the production of IFN (Perdiguero and Esteban 2009). Further, ORF CMLV-CMS-258 encodes a serine proteinase inhibitor 1 (SPI-1), affecting host range, and

ORF CMLV-CMS-258 encodes serine proteinase inhibitor 2 (SPI-2 or CrmA), having antiapoptotic activity and blocking IL-1β and IL-18 processing. CMLV also encodes a complement-binding protein by gene CMLV-CMS-115 which inhibits complement-mediated neutralization and lysis. The genes CMLV-CMS-031 and CMLV-CMS-033 encode virokine/NFkB inhibitor and serine proteinase inhibitor 3 (SPI-3), having antiapoptotic and anti-inflammatory functions, respectively. IL-1β inhibitor of CMLV (encoded by three genes, CMLV-CMS-243, CMLV-CMS-244, and CMLV-CMS-246) has been found to inhibit IL-1β, a potent pro-inflammatory cytokine involved in inflammation.

Although there is lack of information on the expression profile of different cytokines and other immune effector cells, recent studies on the pathogenesis of CMLV in mice model have described the increased level of CD11b + F4/80+ macrophages in the spleen, CD11c + CD8α + in the lymphoid, and CD11c + CD11b + in the myeloid dendritic cell in lymph nodes and interleukin (IL)-6 and IL-18 in the sera of CMLV-infected mice (Duraffour et al. 2011). This indicates the need of detailed investigation of immune effector cells and cytokine profile in camels upon CMLV infection for the development of disease control strategies.

7.5   Risk Factors

Several risk factors are involved in outbreaks of camelpox in susceptible camel population throughout the world. The most predisposing factors for disease outbreaks include introduction of new animals into the herd, common watering, contact with common animal handlers, age of animals (higher incidence in animals less than 4 years old), and rainy season (Khalafalla and Ali 2007). Further, movement of animal herds also facilitates the spread of disease. The transmission of disease occurs mainly by direct contact between infected and susceptible animals or indirectly via contaminated environment. Infection generally occurs through the skin abrasions or via aerosol through inhalation route (Wernery and Kaaden 2002). The feeding of animals on thorny plants sometimes results in abrasion on the skin which provides an easy access for the virus entry, leading to infection. Moreover, poor nutrition and the absence of maternal antibodies along with immunological immaturity in young animals result in infection and heavy mortality (Buller and Palumbo 1991; Kriz 1982). After initial multiplication at local sites, the virus is reported to reach into most of the body secretions, viz., milk, saliva, and nasal and ocular discharges (Ramyar and Hessami 1972). The virus remains alive for at least 4 months in the dried scabs; hence, the environment containing scabs is highly risky for susceptible animals (OIE manual). The disease has got a seasonal trend with higher incidence during the rainy season, possibly associated with higher activity of arthropod vectors involved in transmission. The isolation of CMLV from the tick *Hyalomma dromedarii* further supports this statement (Pfeffer et al. 1996). CMLV has got a limited host range, and outbreak of the disease has not been reported in other animals although antibodies to CMLV have been reported in sheep (6%) and goat (10%) (Housawi 2007). Hence, the possibility of sheep and goat being

asymptomatic carriers of CMLV cannot be excluded. The virulence of infecting strain of the virus also determines the severity of infection and, based on this infection, may range from mild skin lesions to serious systemic infection (Wernery and Kaaden 2002). Upon close contact with infected animals, the human can also be infected with CMLV, and further these infected herdsmen may act as a source of infection to animals (Bera et al. 2011; Khalafalla et al. 2015).

7.6   Transmission

The CMLV is spread by three modes of transmission through direct contact, indirect contact, and insect vectors. The direct transmission of the virus occurs through contacts with sick animals either by inhalation or through skin abrasion. In indirect transmission, a camel becomes infected after contact with the contaminated environment. Infected camels shed the virus through scab materials and secretions like milk, saliva, and ocular and nasal discharges (Ramyar and Hessami 1972) to the environment. The virus particles in the dried scabs may survive for 4 months and contaminate the environment (Elliot and Tuppurainen 2008). Then, the infected environment becomes the source of infection for susceptible animals (Khalafalla and Ali 2007). The possibility of transmission of the disease via an arthropod vector has also been suspected. The CMLV has been isolated from camel ticks (*Hyalomma dromedarii*) recovered from animals with generalized camelpox (Wernery et al. 1997). Thus, it was speculated that the ticks can play a role in spreading the disease from camel to camel. This theory is further supported by the findings of the various studies, which demonstrated that incidences of camelpox infections increase immediately following heavy rains, during which the camel tick population also increases greatly (Wernery and Kaaden 1995). However, whether ticks transmit the disease biologically or mechanically could not be confirmed. Further studies are needed to ensure the involvement of arthropods in the transmission of CMLV (Duraffour et al. 2011).

Transmission of CMLV in unnatural host like humans was also conclusively confirmed in 2009 from India (Bera et al. 2011) (Fig. 7.1) and in 2014 from Sudan (Khalafalla and Abdelazim 2017). The camel herders showed skin infections confined in hands and fingers as reported from India, whereas lesions were found in the

Fig. 7.1 Pock lesion in the finger of animal handler infected with camelpox virus showing typical scab formation

arms, hands, legs, back, and abdomen of camel herder in Sudan. Although earlier few human cases associated with camelpox infection have been reported, no other cases have been verified. It is assumed that CMLV is transmitted to humans via direct contact between infected camels and their human handlers.

7.7   Diagnostics

The presumptive diagnosis of camelpox infection can be made on the basis of clinical symptoms and lesions in the affected animals. However, the disease has to be differentially diagnosed from other poxvirus diseases (contagious ecthyma and papillomatosis), which produce lesions similar to camelpox infection. Several diagnostic methods are available for the detection of camelpox virus, and it is always better to use more than one test for confirmatory diagnosis. Various tests such as cell culture isolation, polymerase chain reaction (PCR) assays, real-time PCR, transmission electron microscopy (TEM), immunohistochemistry, and demonstration of neutralizing antibodies are employed for diagnosis of camelpox.

7.7.1   Clinical Symptoms and Lesions

Typical pock lesions can be seen in the affected camels. The lesions initially appear as papules, further progressing through vesicle, pustules, and finally scab formation (Fig. 7.2). During these period, animal exhibits lymphadenopathy, salivation, pyrexia, lacrimation, and nasal discharge. The lesions initially appear on the skin of the head, eyelids, nostrils, muzzle, and ears. After the development of primary skin lesions, the virus spread to local lymph nodes, and leukocyte-associated viremia occurs. The lesions further extend to the neck, limbs, genitalia, mammary glands, and perineum. In the generalized form, the lesions can be seen all over the body, and, in systemic infection, mucous membranes of the mouth and respiratory and digestive tracts get affected. Although CMLV infection is of benign nature in adult camels, mortality occurs in young animals. Diarrhea and anorexia occur if the

Fig. 7.2 Pock-like lesions on the skin of camel and collection of scabs for laboratory diagnosis

digestive tract is affected. Abortions and stillbirth are observed in pregnant animals, and lactating camel shows reduction in milk yield. Complete healing of skin lesions may take up to 4–6 weeks.

7.7.2 Virus Isolation

CMLV can be propagated in a wide range of cell lines and primary cultures as well as in specific pathogen-free embryonated chicken eggs. The virus can be isolated in 10–13-day-old-specific pathogen-free embryonated chicken eggs by chorioallantoic membrane (CAM) route of inoculation. The inoculated eggs exhibit opaque white proliferative pock lesions (Chauhan and Kaushik 1987; Erster et al. 2018; Marodam et al. 2006) upon incubation at 37 °C for 5 days. The pocks can be excised from the harvested CAM and used for further passaging.

The cell lines, viz., Vero, GMK-AH1, BSC-1, HeLa, and WISH, and primary cultures like lamb testicle, lamb kidney, camel embryonic kidney, fetal dromedary skin cell (Dubca), calf kidney, and chicken embryo fibroblast have been successfully used for propagation of CMLV (Bhanuprakash et al. 2010; Tantawi et al. 1974). However, the CMLV easily replicates in Vero, MA-104, or Dubca cells; hence, these cell lines are generally preferred for primary isolation of CMLV from clinical samples (Pfeffer et al. 1998). While attempting for virus isolation from clinical samples, initial three blind passages in cell lines should be monitored for 7–8 days for cytopathic effects (CPE). After adaptation, the virus produces typical CPE at 3–5 days post infection in the infected cells. The characteristic cytopathic changes include cell rounding, ballooning of cells, vacuolation, syncytia and multinucleated giant cell formation, and degenerative changes **(**Fig. 7.3**)**. The virus also produces intracytoplasmic eosinophilic inclusion bodies in infected cells which can be demonstrated by hematoxylin and eosin staining (Marodam et al. 2006; Pfeffer et al. 1996).
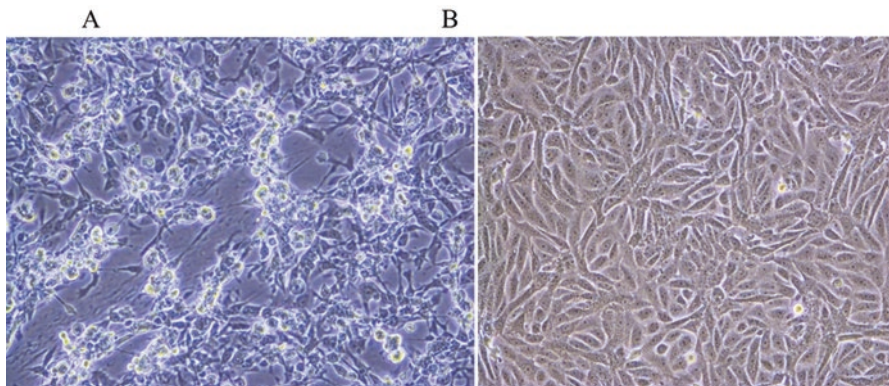

Fig. 7.3 (**a**) Cytopathic effect of CMLV in Vero cells (20X): cell rounding, syncytia formation, cell detachment, and degenerative changes. (**b**) Control healthy Vero cells (20X)

7.7.3   Electron Microscopy

Transmission electron microscopy is employed for direct visualization of viruses in clinical samples as well as in cell culture supernatant. CMLV can be observed as brick-shaped enveloped virus with its outer surface bearing irregularly arranged tubular proteins, which can easily be distinguished from ovoid-shaped parapoxviruses. The diameter of virus particle ranges from $217.6 \pm 18.7 \times 293.15 \pm 18.8$ nm (Erster et al. 2018). The requirement of high concentration of virus in the sample and inability to distinguish CMLV from other OPVs are some of the drawbacks of transmission electron microscopy-based diagnosis.

7.7.4   Serological Test

A wide range of serological tests are available to identify camelpox virus infection of which serum neutralization test is most confirmatory. Polyclonal antibody-based fluorescent antibody test (FAT) and immunoperoxidase test (IPT) can detect the presence of CMLV-specific antibodies; however, there is chance of cross-fluorescence between virus and antisera of other members of the OPV group. However, CMLV can be differentially diagnosed from other related viruses such as capripox, avipox, and parapox viruses using FAT and IPT (Bera et al. 2011; Davies et al. 1975). ELISA has also been employed for detection of CMLV antibodies using semi-purified and purified CMLV antigen. Usage of purified CMLV antigen yielded better results in the form of low background signal with the negative control camel sera (Davies et al. 1975; Munz et al. 1986). The western blot analysis was also used for identification of CMLV-specific protein banding pattern during the early period (Azwai et al. 1996; Pfeffer et al. 1996). However, most of these conventional serological tests are time-consuming and less sensitive. So they are not preferred for primary diagnosis but highly useful in secondary confirmatory diagnosis and retrospective epidemiological studies (Balamurugan et al. 2013).

7.7.5   Molecular Methods

Various molecular tests such as polymerase chain reaction (PCR), PCR-RFLP (PCR-restriction fragment length polymorphism), loop-mediated isothermal amplification (LAMP), and real-time PCR have been developed for rapid and differential diagnosis of CMLV infection. Further, recent advances in sequencing technology particularly next-generation sequencing (NGS) techniques has opened up new vista in the field of disease diagnosis. The NGS is being employed for fast detection of infectious agent along with simultaneous identification of multiple viruses in clinical samples within hours.

7.7.5.1 Polymerase Chain Reaction (PCR)

The currently used conventional PCR assays detect CMLV-specific genomic regions by amplification of various genes like A-type inclusion body (ATI), hemagglutinin (HA), ankyrin repeat protein (C18L) genes, etc. (Balamurugan et al. 2009; Meyer et al. 1997; Ropp et al. 1995). However, in field condition, mixed infections with related viruses are also common. This situation demands a single diagnostic test capable of detecting multiple infectious agents simultaneously rather than detecting each pathogen individually. To overcome this problem, duplex, multiplex, and pan-pox universal PCR assays have also been developed recently (Balamurugan et al. 2009; Li et al. 2010; Khalafalla et al. 2015). The newly developed multiplex PCR is capable of simultaneously detecting three important viruses of camel, i.e., camelpox virus (CMLV), parapox virus, and papilloma virus (Khalafalla et al. 2015). The pan-pox universal PCR assay developed by Li et al. is able to detect most of the members of the family *Poxviridae* (Li et al. 2010). Further, a high-throughput pan-orthopoxvirus detection assay has been developed employing PCR amplification of helicase and polymerase genes followed by electrospray ionization mass spectrometry (PCR/ESI-MS) for rapid identification of each species of OPVs from clinical sample (Eshoo et al. 2009).

7.7.5.2 PCR-Restriction Fragment Length Polymorphism (PCR-RFLP)

This technique employs amplification of specific region(s) by conventional PCR followed by restriction enzyme digestion of PCR products. The difference in band pattern after restriction enzyme digestion helps in specific detection of each virus. The HA and A36R gene-based PCR-RFLP techniques have been developed for specific and differential detection of CMLV from other OPVs (Huemer et al. 2008; Ropp et al. 1995). However, this assay is time-consuming and not being used in most of the diagnostic laboratories nowadays.

7.7.5.3 Loop-Mediated Isothermal Amplification (LAMP)

A highly specific loop-mediated isothermal amplification (LAMP) assay based on C18L gene was developed recently for rapid detection of CMLV (Venkatesan et al. 2012). This assay is proposed to be highly useful in less equipped rural diagnostics laboratory settings of developing countries; however, its large-scale evaluation is undergoing.

7.7.5.4 Real-Time PCR (qPCR)

The real-time PCR has facilitated the detection of minute quantities of viral nucleic acids in a fast and specific manner. In addition, this assay also provide the option to quantify and to genotype the target nucleic acid reliably. Different qPCR-based assays have been developed for specific and differential detection of CMLV. The fluorescence resonance energy transfer (FRET)-based qPCR targeting A13L and rpo18 and viral early transcription factor (VETF) genes have been developed for simultaneous and differential detection of CMLV and other OPVs (Nitsche et al.

2004; Panning et al. 2004). Recently, a SYBR green (Balamurugan et al. 2009) and a TaqMan hydrolysis probe-based qPCR (Venkatesan et al. 2012) assays targeting the ankyrin repeat protein (C18L) gene have also been developed for specific detection of CMLV. The universal TaqMan qPCR assay based on HA and DNA polymerase-E9L genes enables rapid detection of pan-orthopoxviruses (Kulesh et al. 2004).

7.7.5.5 Next-Generation Sequencing (NGS)

The high-throughput sequencing technologies like next-generation sequencing (NGS) using a number of different modern sequencing platforms, viz., Illumina, Roche 454, ion torrent (Proton)/PGM, and SOLiD, enable rapid sequencing-based detection of viruses in clinical samples (Barzon et al. 2011). These sequencing platforms have advantages of sequencing of viral genomes from clinical specimen having mixture of genetic materials and less quantity of virus without needing prior sequence information. Further direct sequencing helps in preventing sequence alteration during in vitro passaging of the virus. The NGS-based diagnostics are not being routinely used in diagnostic laboratories due to the involvement of more cost; however, these techniques are useful for the detection of mixed and unknown infections.

7.8   Prevention and Control

Camelpox can be controlled by reducing exposure to the virus, improving sanitation, and eliminating the vector involved in transmission, immunoprophylaxis, and treatment. To curtail the spread of disease, infected animals should be contained in a separate place and be provided with separate feeding and watering facilities. Care should be taken for young and pregnant animals not to come in contact with infected animals. Personal hygiene of herdsmen and veterinarians is of importance in lowering transmission of CMLV. The personnel caring/treating the infected animal should not be allowed to enter the premises where healthy animals are kept. Newly brought animal should be kept in quarantine for approximately 15–21 days period. Movement of animals should be restricted during outbreak period, and any animal fair should be banned. The vector control is another approach in preventing the transmission of CMLV especially controlling the tick population during rainy season. Tick control with acaricides is only a realistic option for well-managed livestock production facilities; however, this approach has become less reliable, because acaricides are expensive and resistance has developed against many of them. Further, due to the resemblance of CMLV with VARV at molecular level and possibility of CMLV zoonosis, there is a need to follow strict biosecurity and biosafety measures for controlling this transboundary and emerging disease.

7.8.1 Vaccination

Vaccination is the best way to control any viral diseases. Regular vaccination should be practiced in camel herds, particularly before the onset of monsoon, so that animals will have sufficient antibody level before vector population become active. Camelpox vaccines have been developed as prophylactic measures to contain the spread of camelpox in enzootic countries. The CMLV vaccine development was initiated after the eradication of smallpox worldwide. The usage of VACV for the control of OPV infection in animals was not recommended during that period because of the possibility of transmission of VACV to non-vaccinated humans from vaccinated contact animals (Hafez et al. 1992). Therefore, researchers began to focus on developing vaccine against camelpox using CMLV strains that have limited host range (i.e., camels). Both live attenuated and inactivated vaccines are available to control camelpox. Efficacy and safety of three live attenuated (Jouf-78, VD47/25, and Ducapox (298/89)/Ducapox^R) and one inactivated vaccines (CMLV-T8/CAMELPOX^R) have been evaluated thoroughly and are being used for controlling camelpox in different countries (Hafez et al. 1992; Nguyen-Ba et al. 1996; Wernery and Zachariah 1999; Harrak and Loutfi 2000). The live attenuated CMLV Jouf-78 vaccine is being used in Saudi Arabia and has been found to be protective in the field at a dose rate of 10^3 to 10^4 TCID$_{50}$ when given intradermally or subcutaneously (Hafez et al. 1992). The cell culture-based live attenuated CMLV VD47/25 vaccine was found to be innocuous in camels at a dose of $10^{4.7}$ TCID$_{50}$, by subcutaneous route, and is being used in Mauritania (Nguyen Ba et al. 1996). The third live attenuated vaccine Ducapox^R (standing for Dubai CAmelPOX vaccine) has been in use in United Arab Emirates since 1994 with great success. Although there are reports on 6 years of protection upon vaccination, the study was conducted on a very limited number of animals (Wernery and Zachariah 1999). The starting age for vaccination is 6 months. Although a single dose is enough to sustain protection for at least 1 year, booster dose is recommended in 6–9-month-old camels to avoid any vaccine breakdown because of maternal antibody (Khalafalla and Dirdiri 2003). Ducapox^R vaccine is commercially produced in South Africa. The inactivated vaccine against camelpox is derived from CMLV strain T8 isolated from Morocco in 1984. The vaccine is found to be safe and efficacious in young and adult camels. For efficient protection, a second injection is required 1 month post primary vaccination, which is followed by annual booster (Harrak and Loutfi 2000). Recently, a live cell culture attenuated camelpox vaccine has been reported from India, and the thermostability of this vaccine has also been evaluated using various stabilizers which will help in their use in dry and hot camel-rearing regions (Prabhu et al. 2014).

7.8.2   Antiviral Therapy

Antiviral agents inhibit viral replication at the cellular level, interrupting one or more steps involved in the life cycle of the virus. These agents have a limited spectrum of activity, and most of them interrupt host cell function and are toxic to cells at various degrees. Postexposure therapeutic approaches for camelpox infection have got limited use in adult animals; however, this can be useful in young animals which are more susceptible to infection. Only few antiviral agents have been evaluated for their potential use against CMLV in both in vitro and in vivo studies (Duraffour et al. 2007; Smee et al. 2002). The drug molecules found to be effective against CMLV include cidofovir (acyclic nucleoside phosphonate family) and its derivates like CMX001, HPMP-5-azacytozine, and HPMPDAP. In a study conducted in athymic nude mice, cidofovir was found to give 100% protection from morbidity when administered intraperitoneally (once per day for 3 days at 50 mg/kg) as well as topically as 1% cidofovir cream (once per day for 5 days). Another cidofovir analogue HPMP-5-azacytozine has also shown anti-CMLV effect in in vitro studies; however, more detailed study is required to confirm its antiviral activity. The efficacy of the drug CMX001 (lipid derivative of cidofovir) has not been evaluated against CMLV, although the EC_{50} of this drug has been calculated for CPXV (0.6 μM) and VACV (0.8 μM) in human foreskin fibroblasts. Hence, it is assumed that CMX001 will also be active against CMLV within the EC_{50} range (0.6 μM–0.8 μM) reported for CPXV and VACV. The drug ST-246 which was found to be highly effective against OPV infection both in vivo and in vitro has also been evaluated for anti-CMLV activity in vitro. The drug molecule exhibited EC_{50} values of 0.01 μM, 0.05 μM, and 0.08 μM in the cell lines Vero, PHK, and HEL, respectively (Duraffour et al. 2007; Yang et al. 2005).

Despite all these adaptive measures, the success of any prevention and control policy depends on the implementation of an adequate surveillance system. The presence of antibodies to CMLV in sheep and goat and spillover infection to humans reminds us that adaptation of CMLV to other animal species should not be neglected. The role of arthropod vectors in the transmission of camelpox needs to be clearly ascertained by screening tick population collected from goats, sheep, and cattle from countries endemic for the disease. Limited geographical presence of the disease (arid and semiarid regions), host restriction of CMLV, and availability of suitable vaccines make this disease a better candidate for eradication campaign in the near future in similar line with other diseases.

7.9   Conclusion and Future Prospects

In recent times, the increasing number of OPV infections among animals and humans in the different parts of world warrants the focus on stringent research on CMLV. Although the disease was considered inconsequential until recent times, the recent incidences of zoonotic infections in Asian and African countries have brought the disease into limelight. Many researchers believe that two strains of CMLV exist

(virulent one causing systemic infection and less virulent strain causing mild skin lesions); however, more detailed study on genome-level information is required to confirm this hypothesis. The genome of CMLV encodes many gene homologues to those in VARV, VACV, CPXV, and MPXV; however, whether all these genes with putative immunoregulatory functions are functionally active or not have to be ascertained. Unlike other OPV, the pathogenesis of CMLV has not been studied in detail, which is highly required to answer the questions on tissue tropism, limited host range, and spread from the initial site of infection, counter host immune responses, etc. It is also unknown whether any reservoir host exists for CMLV. The presence of antibodies to CMLV in sheep and goat and spillover infection to humans reminds us that adaptation of CMLV to other animal species should not be neglected. Further, the role of arthropod vector in disease transmission has also to be confirmed. For the control of the disease, vaccines have been developed; however, new-generation vaccines for long-term immunity are to be developed. With the present antiviral treatment being a costly affair, cheaper broad-spectrum alternative antivirals may be explored for developing effective therapeutics for disease management. Limited geographical presence of disease (arid and semiarid regions), host restriction of CMLV, and availability of suitable vaccines make this disease a better candidate for eradication campaign in the near future in similar line with other diseases. Usage of vaccines which produce long-lasting immunity (considering the 40–50 years life span of camels) and inclusion of even wild (non-domestic) and Bactrian camels (existing in some Asian countries) in vaccination program with proper health approaches may help in the eradication of the disease.

Conflict of Interest There is no conflict of interest.

References

Abdo el Motalab YS, Ahmed AB (2014) Isolation and identification of camelpox virus in Eastern Sudan SUST. J Agric Vet Sci 15(2):73–81

Abu Elzein EM, Gameel AA, Ramadan RO, Housawi FM (1999) An eruptive moderate form of camelpox infection in dromedary camels (Camelus dromedarius) in Saudi Arabia. Rev Sci Tech 18:749–752

Afonso CL, Tulman ER, Lu Z, Zsak L, Sandybaev NT, Kerembekova UZ, Zaitsev VL, Kutish GF, Rock DL (2002) The genome of camelpox virus. Virology 295:1–9

Alcami A, Smith GL (2002) The vaccinia virus soluble interferon-gamma receptor is a homodimer. J Gen Virol 83:545–549

Alcami A, Symons JA, Collins PD, Williams TJ, Smith GL (1998) Blockade of chemokine activity by a soluble chemokine binding protein from vaccinia virus. J Immunol 160:624–633

Alcami A, Khanna A, Paul NL, Smith GL (1999) Vaccinia virus strains Lister, USSR and Evans express soluble and cell-surface tumour necrosis factor receptors. J Gen Virol 80(Pt 4):949–959

Alcami A, Symons JA, Smith GL (2000) The vaccinia virus soluble alpha/beta interferon (IFN) receptor binds to the cell surface and protects cells from the antiviral effects of IFN. J Virol 74:11230–11239

Alhendi AB, Abuelzein EM, Gameel AA, Hassanein MM (1994) A slow-spreading mild form of camel pox infection. Zentralbl Veterinarmed B 41:71–73

Al-Zi'abi O, Nishikawa H, Meyer H (2007) The first outbreak of camelpox in Syria. J Vet Med Sci 69:541–543

Ayelet G, Jenberie S, Belay A, Mohammed A, Mola B, Gizaw Y, Muhie Y, Gelaye E, Asmare K, Skjerve E (2013) The first isolation and molecular characterization of camelpox virus in Ethiopia. Antivir Res 98:417–422

Azwai SM, Carter SD, Woldehiwet Z, Wernery U (1996) Serology of orthopoxvirus camel infection in dromedary camels: analysis by ELISA and Western blotting. Comp Immunol Microbiol Infect Dis 19:65–78

Balamurugan V, Bhanuprakash V, Hosamani M, Srinivasan VA, Singh RK (2008) Comparative sequence analyses of B5R gene of Indian camelpox virus isolates with other orthopoxviruses. Indian J Virol 19(20):34–38

Balamurugan V, Bhanuprakash V, Hosamani M, Jayappa KD, Venkatesan G, Chauhan B, Singh RK (2009) A polymerase chain reaction strategy for the diagnosis of camelpox. J Vet Diagn Invest 21:231–237

Balamurugan V, Venkatesan G, Bhanuprakash V, Singh RK (2013) Camelpox, an emerging orthopox viral disease. Indian J Virol 24:295–305

Barzon L, Militello V, Lavezzo E, Franchin E, Peta E, Squarzon L, Trevisan M, Pagni S, Dal Bello F, Toppo S, Palu G (2011) Human papillomavirus genotyping by 454 next generation sequencing technology. J Clin Virol 52:93–97

Baxby D (1972) Smallpox-like viruses from camels in Iran. Lancet 2:1063–1065

Baxby D (1974) Differentiation of smallpox and camelpox viruses in cultures of human and monkey cells. J Hyg (London) 72:251–254

Baxby D, Hessami M, Ghaboosi B, Ramyar H (1975) Response of camels to intradermal inoculation with smallpox and camelpox viruses. Infect Immun 11:617–621

Bera BC, Shanmugasundaram K, Barua S, Venkatesan G, Virmani N, Riyesh T, Gulati BR, Bhanuprakash V, Vaid RK, Kakker NK, Malik P, Bansal M, Gadvi S, Singh RV, Yadav V, Sardarilal, Nagarajan G, Balamurugan V, Hosamani M, Pathak KM, Singh RK (2011) Zoonotic cases of camelpox infection in India. Vet Microbiol 152:29–38

Bhanuprakash V, Prabhu M, Venkatesan G, Balamurugan V, Hosamani M, Pathak KM, Singh RK (2010) Camelpox: epidemiology, diagnosis and control measures. Expert Rev Anti-Infect Ther 8:1187–1201

Buller RM, Palumbo GJ (1991) Poxvirus pathogenesis. Microbiol Rev 55:80–122

Chauhan R, Kaushik R (1987) Isolation of camelpox virus in India. Br Vet J 143:581–582

Dahiya SS, Kumar S, Mehta SC, Singh R, Nath K, Narnaware SD, Tuteja FC (2017) Molecular characterization of camelpox virus isolates from Bikaner, India: evidence of its endemicity. Acta tropica 171:1–5

Davies FG, Mungai JN, Shaw T (1975) Characteristics of a Kenyan camelpox virus. J Hyg 75:381–385

Duraffour S, Snoeck R, Krecmerova M, van Den Oord J, De Vos R, Holy A, Crance JM, Garin D, De Clercq E, Andrei G (2007) Activities of several classes of acyclic nucleoside phosphonates against camelpox virus replication in different cell culture models. Antimicrob Agents Chemother 51:4410–4419

Duraffour S, Meyer H, Andrei G, Snoeck R (2011) Camelpox virus. Antivir Res 92:167–186

El Harrak M, Loutfi C (2000) La variole du dromadaire chez le jeune au Maroc. Isolement et identification du virus. Mise au point du vaccin et application à la prophylaxie. Rev Elev Med Vet Pays Trop 53:165–167

Elliot H, Tuppurainen E (2008) Camelpox. Manual of diagnostic tests and vaccines for terrestrial animals, vol. 2, Chap. 2.9.2, pp 177–184

Erster O, Melamed S, Paran N, Weiss S, Khinich Y, Gelman B, Solomony A, Laskar-Levy O (2018) First diagnosed case of camelpox virus in Israel. Viruses 10:78

Eshoo MW, Whitehouse CA, Nalca A, Zoll S, Ecker JA, Hall TA, Pennella TT, Duncan DD, Desai A, Moradi EK, Rudnick K, Libby B, Ranken R, Sampath R, Hofstadler SA, Ecker DJ, Blyn LB

(2009) Rapid and high-throughput pan-orthopoxvirus detection and identification using PCR and mass spectrometry. PLoS One 4:e6342

Falluji MM, Tantawi HH, Shony MO (1979) Isolation, identification and characterization of camelpox virus in Iraq. J Hyg 83:267–272

Gatie JA (2016) Recurrent outbreaks of camel pox in Camelus dromedarius in Dhi-Qar governorate/Iraq. MRVSA 5(special issue). 1st Iraqi colloquium on camel diseases and management):58–63

Gelaye E, Achenbach JE, Ayelet G, Jenberie S, Yami M, Grabherr R, Loitsch A, Diallo A, Lamien CE (2016) Genetic characterization of poxviruses in Camelus dromedarius in Ethiopia, 2011–2014. Antivir Res 134:17–25

Gitao CG (1997) An investigation of camelpox outbreaks in two principal camel (Camelus dromedarius) rearing areas of Kenya. Rev Sci Tech 16:841–847

Gubser C, Smith GL (2002) The sequence of camelpox virus shows it is most closely related to variola virus, the cause of smallpox. J Gen Virol 83:855–872

Gubser C, Bergamaschi D, Hollinshead M, Lu X, van Kuppeveld FJM, Smith GL (2007a) A new inhibitor of apoptosis from vaccinia virus and eukaryotes. PLoS Pathog 3:e17

Gubser C, Goodbody R, Ecker A, Brady G, O'Neill LAJ, Jacobs N, Smith GL (2007b) Camelpox virus encodes a schlafen-like protein that affects orthopoxvirus virulence. J Gen Virol 88:1667–1676

Hafez SM, al-Sukayran A, dela Cruz D, Mazloum KS, al-Bokmy AM, al-Mukayel A, Amjad AM (1992) Development of a live cell culture camelpox vaccine. Vaccine 10:533–539

Higgins AJ, Silvey RE, Abdelghafir AE, Kitching RP (1992) The epidemiology and control of an outbreak of camelpox in Bahrain. Proc 1st Int Camel Conf 101–104

Housawi FMT (2007) Screening of domestic ruminants sera for the presence of anti-camel pox virus neutralizing antibodies. Assiut Vet Med J 53:101–105

Huemer HP, Honlinger B, Hopfl R (2008) A simple restriction fragment PCR approach for discrimination of human pathogenic old world animal orthopoxvirus species. Can J Microbiol 54:159–162

Jezek Z, Kriz B, Rothbauer V (1983) Camel pox and its risk to the human population. J Hyg Epidemiol Microbiol Immunol 27:29–42

Khalafalla AI, Abdelazim F (2017) Human and dromedary camel infection with camelpox virus in Eastern Sudan. Vector Borne Zoonotic Dis 17:281–284

Khalafalla AI, Ali YH (2007) Observations on risk factors associated with some camel viral diseases, Montpellier, pp 101–105

Khalafalla AI, El Dirdiri GA (2003) Laboratory and field investigations of a live attenuated and an inactivated camelpox vaccine. J Camel Pract Res 10:191–200

Khalafalla AI, Mohamed MEM (1998) Camel pox in the Sudan: part 2. Some properties of camelpox viruses isolated in the Sudan. J Camel Pract Res 5(2):235–238

Khalafalla AI, Mohamed MEH, Ali BH (1998) Camel pox in the Sudan: I–Isolation and identification of the causative virus. J Camel Pract Res 5:229–233

Khalafalla AI, Al-Busada KA, El-Sabagh IM (2015) Multiplex PCR for rapid diagnosis and differentiation of pox and pox-like diseases in dromedary camels. Virol J 12:102

Khan FM (2010) Participatory appraisal and scanning surveillance based contagious diseases risk profile of district Rahim Yar Khan (Pakistan). Pak Vet J 30(4):198–202

Khanna ND, Uppal PK, Sharma N, Tripathi BN (1996) Occurrence of pox infections in camels. Indian Vet J 73(8):813–817

Kriz B (1982) A study of camelpox in Somalia. J Comp Pathol 92:1–8

Kulesh DA, Baker RO, Loveless BM, Norwood D, Zwiers SH, Mucker E, Hartmann C, Herrera R, Miller D, Christensen D, Wasieloski LP Jr, Huggins J, Jahrling PB (2004) Smallpox and pan-orthopox virus detection by real-time 3′-minor groove binder TaqMan assays on the roche lightcycler and the cepheid smart cycler platforms. J Clin Microbiol 42:601–609

Lesse AS (1909) Two diseases of young camels. J Trop Vet Sci 4:1–7

Li Y, Meyer H, Zhao H, Damon IK (2010) GC content-based pan-pox universal PCR assays for poxvirus detection. J Clin Microbiol 48:268–276

Mahmoud M, Abo-Elnag T, Osman W, Bassiouny A, Goda AS (2012) Epidemiology and characterization of camel poxvirus in northwest costal area of Egypt. Glob Vet 9:738–744

Marodam V, Nagendrakumar S, Tanwar V (2006) Isolation and identification of camelpox virus. Indian J Anim Sci 76:326–327

Mayer A, Czerny CP (1990) Chapter 4: Camelpox virus. In: Dinter Z, Morein B (eds) Virus infections of vertebrates, Virus infections of ruminants, vol 3. Elsevier Science Publisher B.V, Amsterdam/Oxford/New York/Tokyo, pp 19–22

Meyer H, Ropp SL, Esposito JJ (1997) Gene for A-type inclusion body protein is useful for a polymerase chain reaction assay to differentiate orthopoxviruses. J Virol Methods 64:217–221

Montanuy I, Alejo A, Alcami A (2011) Glycosaminoglycans mediate retention of the poxvirus type I interferon binding protein at the cell surface to locally block interferon antiviral responses. FASEB J 25:1960–1971

Mosadeghhesari M, Oryan A, Zibaee S, Varshovi HR (2014) Molecular investigation and cultivation of camelpox virus in Iran. Arch Virol 159:3005–3011

Moss B (2007) Poxviridae: the viruses and their replication. In: Knipe DM, Howley PM (eds) Fields virology, vol 5. Lippincot Williams & Wilkins, Philadelphia, pp 2905–2945

Moss B (2013) Poxviridae. In: Knipe DM, Howley PM (eds) Fields Virology, 6th edn. Lippincott Williams & Wilkins, Philadelphia, pp 2129–2159

Munz E, Kropp E, Reimann M (1986) Demonstration of antibodies against Orthopoxvirus cameli in sera of East African dromedaries by ELISA. J Veterinary Med Ser B 33:221–230

Narnaware SD, Ranjan R, Dahiya SS (2018) Clinicopathological investigations during an outbreak of camelpox in a dromedary camel herd in India. Comp Clin Pathol 27:1497–1500. https://doi.org/10.1007/s00580-018-2763-9

Nguyen Ba V, Richard D, Gillet JP (1989) Properties of an orthopoxvirus strain isolated from camels in Niger. Revue d'elevageet de medecineveterinaire des pays tropicaux 42:19–25

Nguyen Ba V, Guerre L, Saint-Martin G (1996) Preliminary study of the safety and immunogenicity of the attenuated VD47/25 strain of camelpoxvirus. Revue d'elevageet de medecineveterinaire des pays tropicaux 49:189–194

Nitsche A, Ellerbrok H, Pauli G (2004) Detection of orthopoxvirus DNA by real-time PCR and identification of variola virus DNA by melting analysis. J Clin Microbiol 42:1207–1213

Ommer Dafalla MA, Abdelhamid Elfadil AM (2007) Epidemiologic and clinical features of camelpox in Jazan region, Saudi Arabia. Vet Res 1(3):65–67

Panning M, Asper M, Kramme S, Schmitz H, Drosten C (2004) Rapid detection and differentiation of human pathogenic orthopox viruses by a fluorescence resonance energy transfer real-time PCR assay. Clin Chem 50:702–708

Perdiguero B, Esteban M (2009) The interferon system and vaccinia virus evasion mechanisms. J Interferon Cytokine Res 29:581–598

Pfeffer M, Meyer H, Wernery U, Kaaden OR (1996) Comparison of camelpox viruses isolated in Dubai. Vet Microbiol 49:135–146

Pfeffer M, Wernery U, Kaaden O-R, Meyer H (1998) Diagnostic procedures for poxvirus infections in camelids. J Camel Pract Res 5:1

Prabhu M, Bhanuprakash V, Venkatesan G, Yogisharadhya R, Bora DP, Balamurugan V (2014) Evaluation of stability of live attenuated camelpox vaccine stabilized with different stabilizers and reconstituted with various diluents. Biologicals 42:169–175

Ramyar H, Hessami M (1972) Isolation, cultivation and characterization of camel pox virus. Zentralbl Veterinarmed B 19:182–189

Renner-Muller IC, Meyer H, Munz E (1995) Characterization of camelpox virus isolates from Africa and Asia. Vet Microbiol 45:371–381

Ropp SL, Jin Q, Knight JC, Massung RF, Esposito JJ (1995) PCR strategy for identification and differentiation of small pox and other orthopoxviruses. J Clin Microbiol 33:2069–2076

Sadykov RG (1970) Cultivation of camelpox virus in chick embryos. VirusngBolezniSkh. Zhi'ootnykh Part I:55

Smee DF, Sidwell RW, Kefauver D, Bray M, Huggins JW (2002) Characterization of wild-type and cidofovir-resistant strains of camelpox, cowpox, monkeypox, and vaccinia viruses. Antimicrob Agents Chemother 46:1329–1335

Symons JA, Alcami A, Smith GL (1995) Vaccinia virus encodes a soluble type I interferon receptor of novel structure and broad species specificity. Cell 81:551–560

Tantawi HH, Saban SM, Reda IM, El-Dahaby H (1974) Camelpox virus in Egypt I – isolation and characterization. Bull Epizoot Dis Afr 22:315–319

Tantawi HH, El-Dahaby H, Fahmy LS (1978) Comparative studies on poxvirus strains isolated from camels. Actavirologica 22:451–457

Tefera M, Gebreah F (2001) A study on the productivity and diseases of camels in eastern Ethiopia. Trop Anim Health Prod 33:265–274

Venkatesan G, Bhanuprakash V, Balamurugan V, Prabhu M, Pandey AB (2012) TaqMan hydrolysis probe based real time PCR for detection and quantitation of camelpox virus in skin scabs. J Virol Methods 181:192–196

Wernery U, Kaaden OR (1995) Infectious diseases of camelids. Blackwell Scientific Publications, Oxford, pp 81–88

Wernery U, Kaaden O (2002) Camelpox. In: Infectious diseases in camelids, vol 2. Blackwell, Berlin

Wernery U, Zachariah R (1999) Experimental camelpox infection in vaccinated and unvaccinated dromedaries. Zentralbl Veterinarmed B 46:131–135

Wernery U, Meyer H, Pfeffer M (1997) Camel pox in the United Arab Emirates and its prevention. J Camel Pract Res 4(2):135–139

Yang G, Pevear DC, Davies MH, Collett MS, Bailey T, Rippen S, Barone L, Burns C, Rhodes G, Tohan S, Huggins JW, Baker RO, Buller RL, Touchette E, Waller K, Schriewer J, Neyts J, DeClercq E, Jones K, Hruby D, Jordan R (2005) An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. J Virol 79:13139–13149

Yousif AA, Al-Naeem AA (2011) Molecular characterization of enzootic camelpox virus in the Eastern Kingdom of Saudi Arabia. Int J Virol 7:135–146