Cross-species transmission of canine distemper virus—an update

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ABSTRACT

Canine distemper virus (CDV) is a pantropic morbillivirus with a worldwide distribution, which causes fatal disease in dogs. Affected animals develop dyspnea, diarrhea, neurological signs and profound immunosuppression. Systemic CDV infection, resembling distemper in domestic dogs, can be found also in wild canids (e.g. wolves, foxes), procyonids (e.g. raccoons, kinkajous), ailurids (e.g. red pandas), ursids (e.g. black bears, giant pandas), mustelids (e.g. ferrets, minks), viverrids (e.g. civets, genets), hyaenids (e.g. spotted hyenas), and large felids (e.g. lions, tigers). Furthermore, besides infection with the closely related phocine distemper virus, seals can become infected by CDV. In some CDV outbreaks including the mass mortalities among Baikal and Caspian seals and large felids in the Serengeti Park, terrestrial carnivores including dogs and wolves have been suspected as vectors for the infectious agent. In addition, lethal infections have been described in non-carnivore species such as peccaries and non-human primates demonstrating the remarkable ability of the pathogen to cross species barriers. Mutations affecting the CDV H protein required for virus attachment to host-cell receptors are associated with virulence and disease emergence in novel host species. The broad and expanding host range of CDV and its maintenance within wildlife reservoir hosts considerably hampers disease eradication.

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Introduction

Morbilliviruses belong to the family *Paramyxoviridae* and include a number of highly pathogenic viruses, such as measles virus, rinderpest virus, canine distemper virus (CDV), and *peste-des-petits*-ruminants

virus, which cause devastating diseases in humans and animals. In the last decades, morbilliviruses emerged also as causative agents of several mass-mortalities in marine mammals [1,2]. Canine distemper is a fatal disease of dogs with a worldwide distribution [3]. The causative agent, CDV, is an enveloped, negative-sense, single-stranded RNA virus. Similar to other paramyxoviruses the virus contains six structural proteins, termed nucleocapsid (N), phospho (P), large (L), matrix (M), hemagglutinin (H) and fusion (F) protein, and two accessory non-structural proteins (C and V) that were found as extratranscriptional units within the P gene [4]. Generally, CDV exhibits lympho-, neuro- and epitheliotropism resulting in systemic infection of almost all organ systems including respiratory, digestive, urinary, lymphatic, endocrine, cutaneous, skeletal and central nervous system (CNS) [5,6]. The disease course and pathogenesis in canine distemper resemble those of human measles virus infection including, fever, rash, respiratory signs, lymphopenia, and profound immunosuppression with generalized depletion of lymphoid organs during the acute disease phase [7]. In addition, CDV infection shows a high incidence of neurological complications [5].

Unlike the related measles virus which is maintained by single host species, CDV represents a rather promiscuous agent causing distemper-like pathology in a variety of different carnivorous and also non-carnivorous species [8–10]. Clinical findings and pathology resemble largely the disease in dogs. However, morbidity and mortality may vary greatly among animal species. Phylogenetic and molecular evolutionary analyses of CDV have revealed that mutations affecting the binding site of the H protein for virus entry receptors (*signaling lymphocytic activation molecule* [SLAM, CD150] and nectin-4) are associated with the occurrence of disease emergence in novel host species [11–15].

The aim of the present article is to give an updated overview of interspecies transmission of CDV and the pathogenesis of distemper in different mammalian species.

Distemper in carnivore species

Domestic dogs

The pathogenesis of CDV infection in domestic dogs has been extensively reviewed previously [3,5]. In brief, disease duration and severity in domestic dogs depends mainly on the animal's age and immune status and strain virulence. The primary mode of infection is via inhalation [16]. Initially, CDV replicates in lymphoid tissue of the upper respiratory tract. Here, monocytes and macrophages are the first target cells which propagate the virus [17]. Following a variable incubation period (one to four weeks), animals develop a characteristic biphasic fever [16,18]. During the first viremic phase, generalized infection of lymphoid tissues with lymphoid depletion, lymphopenia and transient fever is observed. Profound immunosuppression is a consequence of leukocyte necrosis, apoptosis and dysfunction [16,19,20]. Second viremia is associated with high fever and infection of parenchymal tissues such as the respiratory tract, digestive tract, skin, and CNS [16,17]. During this disease stage, various clinical manifestations may be present such as conjunctivitis, nasal discharge, anorexia, respiratory signs, gastrointestinal signs, and neurological deficiencies [16]. Respiratory signs are a sequel of virus-induced rhinitis and interstitial pneumonia, while vomiting, diarrhea and dehydration are caused by gastrointestinal tract infection [21]. Often enteric and respiratory signs are worsened by secondary bacterial infections. Characteristic dermal manifestations include pustular dermatitis (distemper exanthema) and hyperkeratosis of foodpads and nasal planum (hard pad disease). In young animals also enamel hypoplasia and metaphyseal osteosclerosis have been described following CDV infection [22]. Neurologic signs depend on viral distribution in the CNS and include hyperesthesia, cervical rigidity, seizures, cerebellar and vestibular signs, as well as paraparesis or tetraparesis with sensory ataxia [9,23]. Histological manifestations include polioencephalitis and demyelinating leukoencephalomyelitis [24,25]. Recovery depends on the host immune response. Particularly, a strong and effective cellular immune response can eliminate the virus prior to infection of parenchymal tissues, while weak and delayed cellular and humoral immune responses lead to virus spread and persistence, respectively [5,16,26].

Wild canids

Besides domesticated dogs natural and/or vaccine-induced CDV-associated disease has been reported in almost all genera of the tribus true canids. Affected members of the genus Canis include Australian dingos (*Canis dingo*) [27], coyotes (*Canis latrans*) [28,29], black-backed jackals (*Canis mesomelas*) [30], golden jackals (*Canis aureus*) [31], Canadian wolves (*Canis lupus*) [32], American gray wolves (*Canis lupus*) [33], Mexican wolves (*Canis lupus baileyi*) [34], Iberian wolves (*Canis lupus*) [35], and Apennine wolves (*Canis lupus*) [36]. Phylogenetic analyses suggest a CDV spillover from domestic dogs to free-ranging jackals and wolves [30,35]. Referring to this, sequencing of CDV from Apennine wolves in Italy identified a strain belonging to the Arctic lineage, known to circulate in European dog populations [36]. The Ethiopian wolf (*Canis simensis*) is recognized as the rarest canid species in the world and the most threatened carnivore in Africa. This species is almost extinct due to combined effects of rabies and CDV infections [37]. Wolf-derived CDV from the Ethiopian outbreak show sequence homologies to isolates from domestic dogs in the USA, Germany and Japan, suggestive of global virus spread [37]. There is serological evidence of CDV exposition to maned wolves (*Chrysocyon brachyurus*) in Brazil. Natural clinical distemper has not been reported in this species [38], but vaccination-induced distemper may occur [39]. Similarly, there are no reports about cases of naturally occurring distemper in bush dogs (*Speothos venaticus*), however, a possible vaccine-induced case has been described [40].

Endangered African wild dogs (*Lycaon pictus*) have been reported to be exposed to CDV and are highly susceptible to develop distemper [41, 42]. Molecular analyses of isolates from African wild dogs suggest that CDV is endemic in wildlife carnivore populations in Tanzania (Serengeti ecosystem) [43,44]. Lethal lesions include interstitial pneumonia and suppurative to necrotizing bronchopneumonia with viral inclusion bodies and syncytial cells [43,44]. Besides natural infection, African wild dogs in captivity may also succumb to vaccine-induced canine distemper [45].

All genera of the tribus true foxes, i.e. *Vulpes* sp., including *Vulpes lagopus* (syn. *Alopex lagopus*), *Urocyon* and *Otocyon*, are susceptible to CDV infections and may develop clinical disease. CDV infections have been reported in red foxes (*Vulpes vulpes*) from various European countries including Germany [46,47], Italy [48,49], Spain [50], and Portugal [51]. Disease has been reported also in swift foxes (*Vulpes velox*) [52], kit foxes (*Vulpes macrotis*) [52], Indian foxes (*Vulpes bengalensis*) [53], and fennec foxes (*Vulpes zerda*) [54]. Infected foxes show abnormal behavior including loss of fear for humans, disorientation, and/or respiratory distress. Morphologic findings comprise mainly conjunctivitis, pustular dermatitis, lymphohistiocytic polioencephalitis, and bronchointerstitial pneumonia with viral inclusion bodies and syncytia [14].

Recently, the emergence and spread of a single genetic cluster within the Europe-1 clade of CDV among foxes and other wild carnivores in the Alpine region has been reported indicating the ability of this virus to replicate in a wider host range [55]. In gray foxes (*Urocyon* sp.), CDV outbreaks might have caused a dramatic population decline of Santa Catalina Island foxes (*Urocyon littoralis catalinae*). Sequence analyses indicate virus transmission from infected mainland USA raccoons unintendedly introduced to the island [56]. Mainland gray foxes (*Urocyon cinereoargenteus*) are susceptible to natural distemper and vaccine-induced distemper [57]. Crab-eating foxes (*Cerdocyon thous*) show neurological signs and succumb to CDV infection [58]. Free-ranging culpeo (*Dusicyon culpaeus*) and South American gray foxes (*Dusicyon griseus*) have been exposed to CDV [59]. Similarly, in the Serengeti-Mara ecosystem of East Africa, bat-eared foxes (*Otocyon*

megalotis) have succumbed to CDV during epidemics [60]. Serological evidence of CDV infection or fatal CDV infection have been observed in various *Pseudalopex* sp. [61], Pampas gray foxes (*Lycalopex gymnocercus*) [62], and hoary foxes (*Lycalopex vetulus*) [63].

The raccoon dog (*Nyctereutes procyonoides*) originally distributed in East Asia represents a recently established neozoon in Germany and neighboring countries [64]. This wild omnivore serves as host and vector for parasites and other pathogens including CDV [64]. Raccoon dogs are highly susceptible to CDV infection [65] showing similar morphological changes as infected domestic dogs including interstitial pneumonia, demyelinating encephalitis, lymphoid depletion in various lymphoid tissues and catarrhal or necrotizing gastroenteritis [66]. The emergence of CDV strains belonging to the Asia-1 genotype with two amino acid substitutions in the H protein isolated from raccoon dogs and other carnivores in China resulted in clinical distemper even in vaccinated animals [67].

Procyonids

The raccoon is native to North America and a neozoon in continental Europe and Japan [68,69]. Serological surveys revealed CDV exposition of members of the family *Procyonidae* including predominantly raccoons (*Procyon lotor*) [70], but also pygmy racoons (*Procyon pygmaeus*) [71]. Spontaneous clinical distemper has been reported in sylvatic and urban populations of raccoons [68,72], while vaccination-induced distemper is reported in kinkajous (*Potos flavus*) [73]. Clinical signs in raccoons resemble those in dogs and must be differentiated from rabies in cases with neurologic signs [72]. Pathology is characterized by blepharoconjunctivitis, rhinitis, occasional pigmentation of the muzzle and footpads with hyperkeratosis, interstitial pneumonia with syncytia and viral inclusion bodies, and demyelinating cerebellar white matter disease [68,72,73]. Lednicky et al. (2004) identified two different American CDV lineages causing raccoon distemper outbreaks in the same area suggesting multiple reintroductions of the virus [74]. Phylogenetic analyses of CDV isolates from an outbreak in free-ranging raccoons in Germany from 2012 to 2013 revealed close relations with European CDV lineages especially from foxes and domestic dogs suggestive of interspecies transmission [68]. In addition, raccoons might have intensified transmission of Asia-1 lineage CDV during an epidemic in wildlife mammals in Japan (2007–2008) [65,69].

Ailurids

Red pandas (*Ailurus fulgens*) are susceptible to CDV infection. A fatal disease clinically similar to canine distemper occurred after vaccination with modified live distemper vaccine [75]. Giant cell pneumonia and viral inclusion bodies in pulmonary and digestive tract epithelium were found histologically [75].

Ursids

There is marked serological evidence that various species of bears have been exposed to CDV including American black bears (*Ursus americanus*) [76], Asian black bears (*Ursus tibethanus*) [66], polar bears (*Ursus maritimus*) [77], grizzly bears (*Ursus arctos horribilis*) [32] and Marsican brown bears (*Ursus arctos marsicanus*) [78]. However, clinico-pathological manifestation of distemper in ursids is rare. An American black bear yearling showed loss of fear for humans, periods of somnolence, sporadic tremors and seizures caused by nonsuppurative polioencephalitis with eosinophilic intranuclear and cytoplasmic inclusion bodies in neurons. Additionally, hyperkeratotic thickened footpads were recorded. Sequence homologies with a CDV vaccine strain (Rockborn strain) indicate the potential virus exchange between vaccinated domestic animals and wildlife [79]. Furthermore, neonatal death of polar bears (*Ursus maritimus*) and a spectacled bear (*Tremarctos ornatus*) has been attributed to CDV infection [80]. The virus can be transmitted to bears by dogs, mustelids, coyotes, and other carnivores that might be sympatric with bears. Besides serological evidence of CDV infection in captive Giant pandas (*Ailuropoda melanoleuca*) [81], also fatal CDV infection was noted recently among these endangered species in a wildlife rescue and breeding center in China [82].

Mustelids

Domestic ferrets (*Mustela putorius furo*) are highly susceptible to CDV infection with a mortality rate of up to 100% in non-vaccinated populations. As a consequence of systemic infections, ferrets develop high fever together with respiratory and intestinal signs [83]. Classical dermal manifestations include reddening and crusting of chin and mouth and progressive hyperkeratosis of nose and footpads. Polioencephalitis leading to behavioral changes, lethargy and seizures is a common cause of death or reasons for euthanasia. But CNS manifestation varies among CDV isolates and is preferentially caused by strains known to be neurovirulent in dogs (e.g. Snyder Hill and Cornell A75-17) [84,85]. In addition, profound generalized lymphoid depletion can be observed in affected animals [86].

First reports of CDV infection in farmed minks (*Neovison vison*) have been described in 1930 [87]. Similar to ferrets, young minks usually die suddenly, while adult mink have an increased resistance and exhibit protracted disease courses with neurological signs [88]. Recently, phylogenetic analyses showed that wildlife species in Denmark, such as foxes, potentially contribute to the transmission of CDV to farmed mink and that the virus is able to be maintained in the wild animal reservoir between outbreaks. Isolates from the Danish outbreak in 2012 clustered in the European CDV lineage and were closely related to viruses circulating in wildlife populations from Germany and Hungary [89]. Interestingly, identification of CDV in fleas collected from a mink carcass has led to speculations about vector-mediated transmission of viruses between mink and other species [89].

Systemic, often lethal disease has been observed in black-footed ferrets (*Mustela nigripes*) following CDV infection representing a serious threat for wildlife and captive populations [90]. Noteworthy, severe pruritus can be commonly observed as an initial clinical sign in affected animals, followed by hyperkeratosis and progressive loss of body condition. The high susceptibility of black-footed ferrets is demonstrated also by their fatal response to modified-live CDV vaccines demonstrated to be safe in domestic ferrets and Siberian polecats [91]. Mortalities following CDV infection have been described also in colonies and wildlife populations of other mustelids, including martens (Fig. 1), polecats, badgers, ferret-badger, otters, and weasels, leading to the assumption that all members of the family are susceptible [10,92]. At post mortem examination interstitial pneumonia, enteritis, encephalitis (Fig. 2) and lymphoid depletion (Fig. 3) with intralesional virus antigen can be found. Common lethal complications in mustelids are secondary parasitic or bacterial diseases (Figs. 4 and 5) as a consequence of virus-induced immunosuppression [86]. Mustelids are regarded as a CDV reservoir and potential source of transmission to other species, including domestic dogs. Phylogenetic analyses revealed a co-circulation of several contemporary CDV genotypes in carnivores of central Europe with the occurrence of a distinct CDV lineage in ferrets, polecats and martens, suggestive of mustelid-adapted strains [93]. As in other carnivores distemper represents an important differential diagnosis for other CNS infections and has to be discriminated especially from rabies [94]. Distemper has been described also in striped skunks (*Mephitis mephitis*) belonging to the mustelid related *Mephitidae* family [95].

Felids

In felids, CDV can cause clinically silent infections or fatal disease. Although CDV antibodies have been detected in domestic cats (*Felis catus*) [96], there are no reports of naturally occurring systemic CDV infections, despite frequent contact with dogs. Experimental infection of domestic
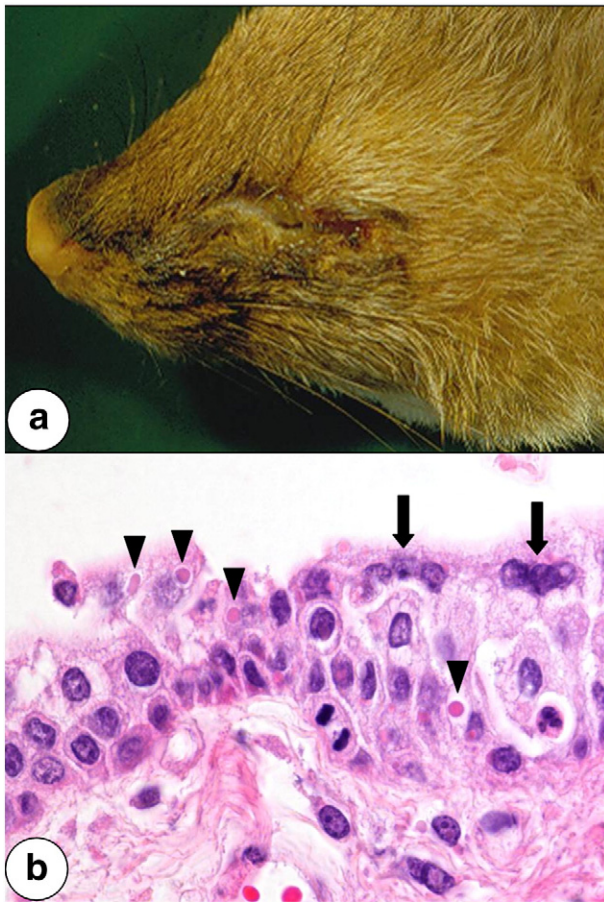
Fig. 1. Canine distemper virus infection in a marten. a) Severe muco-suppurative conjunctivitis; b) Conjunctiva with epithelial syncytial cells (arrows) and cytoplasmic eosinophilic viral inclusion bodies (arrowheads); hematoxylin–eosin, magnification ×600.
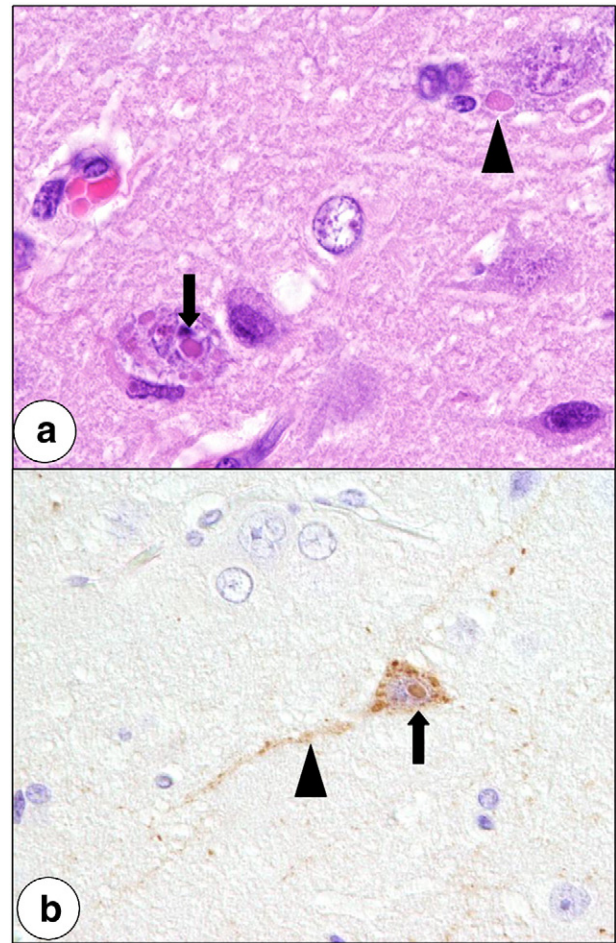

Fig. 2. Encephalitis in a badger following canine distemper virus (CDV) infection. a) Intranuclear (arrow) and cytoplasmic eosinophilic viral inclusion bodies in neurons of the cerebral cortex; hematoxylin–eosin, magnification ×1000; b) Immunolabeling of CDV antigen in the nucleus (arrow) and neuronal cytoplasmic process (arrowhead); avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×600.

cats with a highly virulent CDV strain resulted in asymptomatic infection without virus shedding [97], and specific pathogen free cats inoculated with homogenized tissues from a leopard that died of CDV infection showed no clinical signs except transient leukopenia [98]. Recently, an unusual cutaneous CDV infection associated with concurrent orthopoxvirus infection has been reported in a cat [99]. Wild (*Felis silvestris silvestris*) and feral cats (*Felis silvestris catus*) from Portugal show evidence of low exposition to CDV [100].

CDV-neutralizing antibodies have been found in various species of wild felids throughout their natural habitats worldwide, e.g. in Amur tiger (*Panthera tigris altaica*) [101], leopard (*Panthera pardus*) [102] or South American jaguars (*Panthera onca*) [103]. The first devastating epidemic in large wild felids occurred in 1994 within the Serengeti-Mara ecosystem of East Africa. Approximately one-third of the Serengeti lion population (*Panthera leo*) died or disappeared. Analyses indicated that the Serengeti lion CDV was closely related to the Onderstepoort strain isolated from a domestic dog in South Africa. Clinically, grand mal seizures and myoclonia were observed. Death was caused by nonsuppurative encephalitis and pneumonia [60]. A similar epidemic occurred in 2001 in the Ngorongoro Crater lion population [104]. In east Africa, CDV-infected domestic dogs are regarded as the main source for infection in lions. However, since widespread dog vaccination reduces outbreak sizes but does not prevent CDV transmission to Serengeti lion populations, the virus is supposed to be maintained also in wildlife hosts, e.g. in hyenas and jackals [105]. CDV infection in lions is not necessarily fatal, because retrospective serological investigations revealed that at least five "silent" CDV epidemics swept through the same two lion populations between 1976 and 2006 without clinical disease or increased mortality [106]. Severe hemoparasitism with tick-

born *Babesia* sp. triggered by extreme drought is regarded as a major contributing factor to fatal outcome of the epidemics in 1994 and 2001 [106]. CDV represents also a threat for the wild Amur tiger (*Panthera tigris altaica*), one of the most endangered cat populations. CDV-infected animals show clear nasal and ocular discharge, stupor and anorexia. Neurological signs include non-responsiveness to stimuli, blindness, absent fear for humans, head pressing, ataxia, and intermittent petit and grand mal seizures. Lymphopenia indicates immunosuppression in affected tigers. Contrary to histologic lesions in domestic dogs, diffuse alveolar type II cell hyperplasia with cytoplasmic and intranuclear viral inclusion bodies is found in the lungs of large felids [107]. Additionally, in the brain typical white matter lesions seen in canids are lacking, but instead lymphocytic meningoencephalitis with extensive malacia in brainstem, cerebellum, and thalamus are observed. Viral inclusion bodies and antigen are detectable in glial cells and occasional neurons in malacic areas [107]. Sequence analyses showed homologies between tiger CDV and Arctic-like strains of CDV isolated in Baikal seals in Russia and domestic dogs [107]. Moreover, phylogenetic analysis and molecular characterization of CDV strains from a variety of geographic lineages and with a variety of amino acid residues in the H gene binding site indicate that some strains are regularly capable to infect felids and cause diseases. Therefore, CDV infections of felids may not just be incidental events or spillover diseases but a part of the regular host spectrum of this infectious disease [101].

Similar to infections in wildlife populations, large felids including tigers (*Panthera tigris*), lions (*Panthera leo*), leopards (*Panthera pardus*),
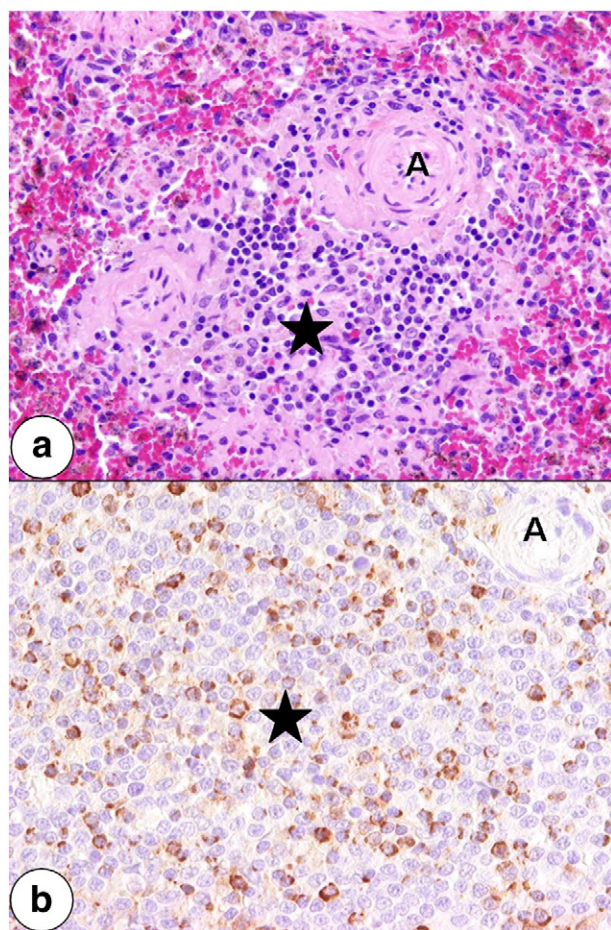
Fig. 3. Lymphoid depletion in wildlife species following canine distemper virus (CDV) infection. a) Severe hypocellularity (asterisk) of the splenic white pulp in a CDV-infected marten; A = central artery; hematoxylin–eosin, magnification ×200; b) Detection of CDV antigen in a splenic follicle of a raccoon by immunohistochemistry; A = central artery; avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×400.

and jaguars (*Panthera onca*) in zoological collections may become infected with CDV. Animals often develop fatal disease with respiratory and gastrointestinal signs followed by neurological manifestation [66, 108]. Possible sources of the virus in zoo outbreaks are small carnivores, such as raccoons or raccoon dogs that may come in contact with captive cats [66,108]. Usually CDV spreads through aerosol droplets and contact with infected body fluids, but felids may become also infected by predation, e.g. exposure to unvaccinated and infected domestic dogs or other wild susceptible hosts [66,108].

CDV infections have been also reported in members of the genus *Lynx* including the highly endangered Iberian lynx (*Lynx pardinus*) [109], the Eurasian lynx (*Lynx lynx*) [14], the Canadian lynx (*Lynx canadensis*) [110], and bobcats (*Lynx rufus*) [110]. CDV was reported as the etiological agent of encephalitis in a Canadian lynx [110].

There is serological evidence of CDV infections in Namibian free ranging and captive cheetahs (*Acinonyx jubatus*) [102], Namibian caracals (*Caracal caracal*) [102], Argentinian Geoffroy's cats (*Leopardus geoffroyi*) [111], Brazilian pumas (*Puma concolor*) [112], and Californian mountain lions (*Puma concolor*) [113].

Viverrids

Members of the family *Viverridae* including the Binturong (*Arctictis binturong*) [114], masked palm civet (*Paguma larvata*) [115], Asian palm civet (*Paradoxurus hermaphroditus*) [115], small Indian civet

(*Viverricula indica*) [115], and genet (*Genetta genetta*) [116] are susceptible to CDV and develop clinical disease. Infected animals show neurological signs, dyspnea, oculonasal discharge, diarrhea, alopecia, and thickened hyperkeratotic and scaling footpads [114]. Morphological lesions comprise bronchointerstitial pneumonia with syncytial cells, vesiculopustular dermatitis, hyperplastic pododermatitis with necrosis, lymphoid depletion as well as leuko- and polioencephalitis with intralesional viral antigen [114–116].

Hyaenids

Free-ranging Serengeti hyenas (*Crocuta crocuta*) and captive hyenas may succumb following CDV infection (Fig. 6). Sequence data revealed closest homology to CDV strains causing high mortality in sympatric lions [117]. Seropositivity of living animals indicates that Serengeti hyenas may also become subclinically infected without overt disease or can recover from disease, respectively [118]. Similarly, CDV exposure has been reported from Zambian hyenas [41].

Distemper in non-carnivore species

The remarkable ability of CDV to cross species barriers is exemplified by its infection of non-carnivore species such as peccaries and non-human primates. In 1989, a CDV epizootic with fatal encephalitis was observed in collared peccaries (javelina; *Pecari tajacu*) in the desert of southern Arizona (USA) [119]. Serological surveys suggest that CDV is enzootic in free-ranging peccaries of this area and that animals usually recover from infection. Thus, increased fatality rate during the outbreak was probably supported by high population densities and crowding around remaining water sources [120]. CDV-neutralizing antibodies suggestive of subclinical infection have been detected also in wild boars and Sika deer during an epidemic in different wildlife mammals in Japan [65].

In 1989, first cases of natural CDV infections in Japanese macaques (*Macaca fuscata*) with two fatalities were reported [121]. In 2006, large CDV outbreaks occurred among rhesus monkeys (*Macaca mulatta*) in a breeding farm in Guangxi province (China) with death rates up to 30% (about 4000 fatalities). Animals displayed measles-like signs, such as respiratory distress, anorexia, fever, rash and conjunctivitis. Although the exact source of infection could not be determined, virus transmission by contact between farm monkeys with local wild monkeys or a spillover from a stray dog carrying CDV that became adapted to the new host was discussed [122]. CDV infection of twenty rhesus monkeys in an animal center in Beijing (China) was likely associated with this outbreak [123]. In a subsequent CDV outbreak in Japan in 2008, similar fatality numbers and febrile systemic diseases were observed in colonies of long-tailed macaques (*Macaca fascicularis*). Post mortem examination revealed interstitial pneumonia, generalized lymphoid depletion and demyelination in the brain. Sequence analyses of the viral genome revealed that Chinese and Japanese isolates are closely related within the Asia-1 clade, suggesting continuous chains of CDV infection in monkeys [124].

Expansion of host species to include primates has raised concerns about a potential risk of CDV infection in humans. It has been demonstrated *in vitro* that the monkey-adapted strain (CYN07-dV) has an intrinsic ability to use human nectin-4 for virus entry and easily become adapted to use the human CD150 following minimal amino acid changes of the viral H protein [125]. Thus, species jumps to human beings, especially in people with a lack of cross-protective measles immunity are proposed to happen in the future [12,126,127]. Moreover, the participation of CDV in the pathogenesis of Paget's disease of bone and multiple sclerosis in human beings has been speculated but lacks final verification [3,128].
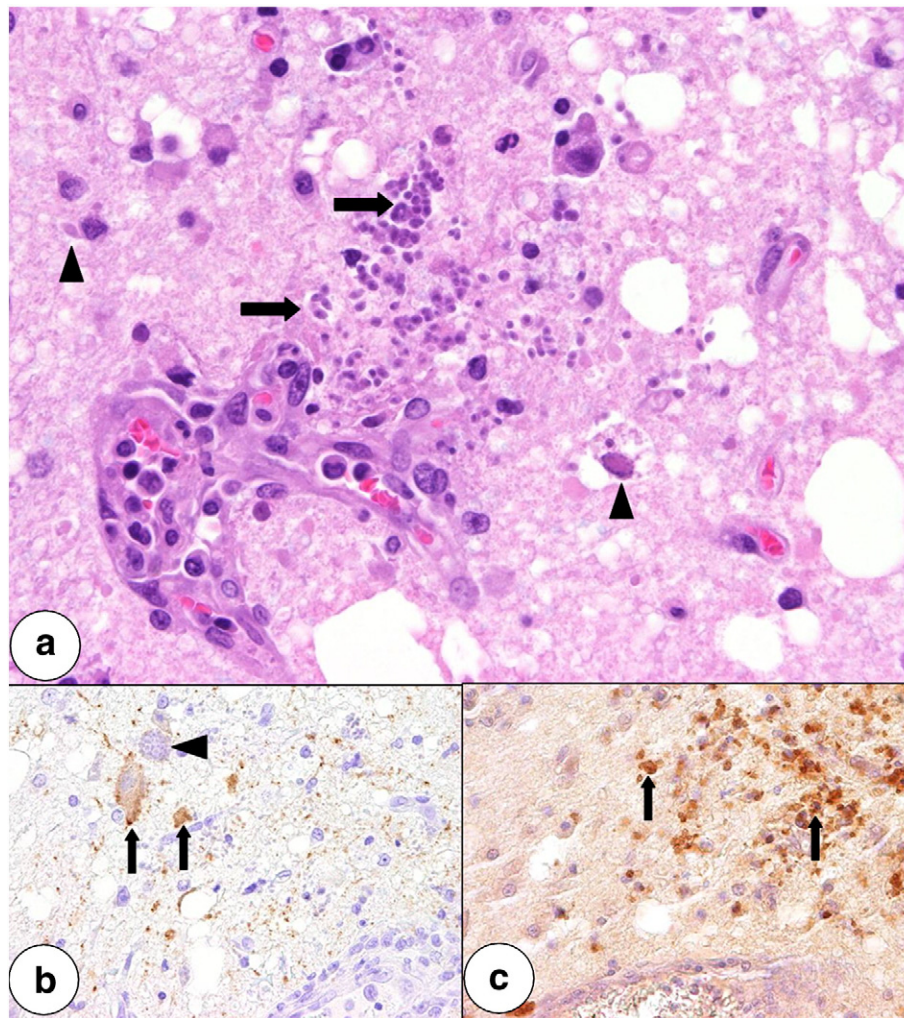
Fig. 4. Concurrent toxoplasmosis in a marten infected with canine distemper virus (CDV). a) lympho-histiocytic encephalitis with numerous protozoal tachyzoites (arrows) and intranuclear eosinophilic viral inclusion bodies (arrowheads); hematoxylin–eosin, magnification ×400; b) Immunolabeling of CDV antigen in neurons and glial cells (arrows); note accumulation of protozoal tachyzoites (arrowhead); avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×400; c) Immunolabeling of *Toxoplasma gondii* antigen (arrows); avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×400.

Canine distemper virus and other morbilliviruses in marine mammals

Several morbillivirus epidemics have been observed in different marine mammal species. Distemper in seals can be caused by CDV and the closely related but genetically different phocine distemper virus (PDV) [129]. The devastating PDV epidemic among harbor seals (*Phoca vitulina*) and gray seals (*Halichoerus grypus*) in northwestern European waters in 1988 represents the first documented disease manifestation of a morbillivirus infection in marine mammals [130]. At the same time, epidemics with CDV strains of the Arctic group were observed among Baikal seals (*Phoca sibirica*) in Siberia [131]. CDV was isolated also from Caspian seals during disease outbreaks with high mortality rates in 1997, 2000 and 2001 [132–134].

Experimental infection revealed duration of phocine distemper ranging from two to three weeks with a mortality rate of 60% to 80% [135]. Similar to CDV, PDV infection of seals leads to interstitial pneumonia and catarrhal enteritis, causing fever, diarrhea, coughing, and dyspnea [135]. Other signs include nasal discharge, ocular discharge, anorexia, weight loss and abortion [136]. Common neurological manifestations represent tremor, behavioral changes and lethargy [129]. Brain lesions in PDV-infected seals are similar to CDV-induced acute polioencephalitis in dogs and measles virus inclusion body

polioencephalitis in human beings, respectively. With disease progression also demyelination in the CNS can be observed [137,138]. Typical findings in PDV-infected seals include lymphoid depletion in spleen and lymph nodes with inclusion bodies and syncytial cells [136] and thymic atrophy, which renders the animals susceptible to develop opportunistic infections. Interestingly, few harbor seals develop also epidermal hyperplasia and hyperkeratosis as a consequence of dermal infection [139].

Surprisingly, PDV has been isolated only during the epidemics in northwestern European waters in 1988 and 2002 [129,137]. In some CDV outbreaks including the mass mortalities among Baikal and Caspian seals, terrestrial carnivores including dogs and wolves have been suspected as vectors for the infectious agent [140]. Different hypotheses concerning the origin of PDV and its geographical and chronological dissemination pattern have been presented. These include virus spread from less susceptible marine mammals including Canadian harp seals (*Phoca groenlandica*) and Baltic gray seals (*Halichoerus grypus*), as well as infection from diseased terrestrial animals including minks, wolves and polar bears. Debated predisposing factors for disease outbreaks include malnutrition and immunosuppressive xenobiotics [141,142]. It still remains a possibility that PDV strains, with reduced virulence for terrestrial mammals, are circulating in these species and cause mass die-offs in pinnipeds after crossing the species barrier [143,144].
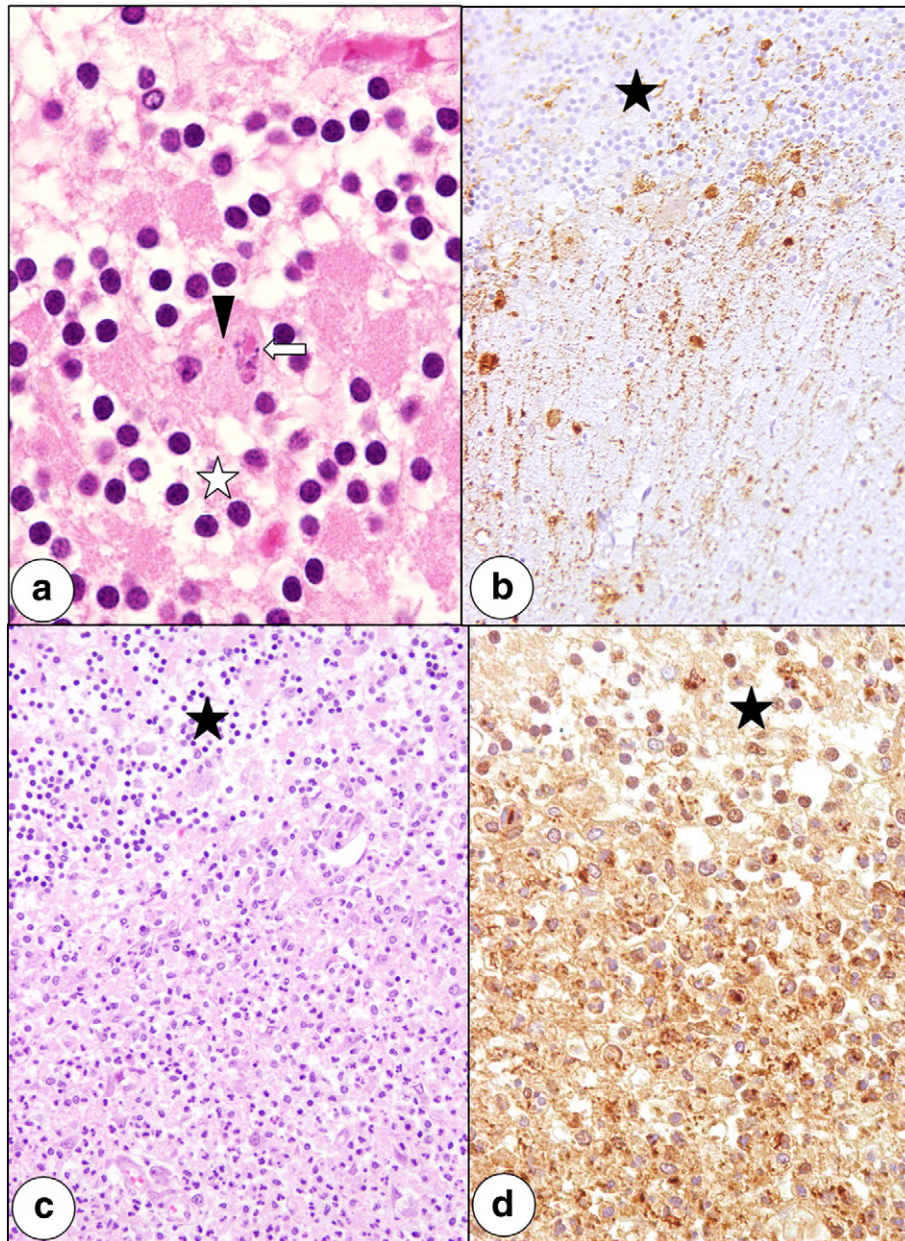
Fig. 5. Bacterial co-infection in a canine distemper virus (CDV) infected badger. a) Intranuclear (arrow) and cytoplasmic (arrowhead) inclusion bodies in the granular layer (asterisk) of the cerebellum; hematoxylin–eosin, magnification ×600; b) Immunohistochemical labeling of CDV antigen in the cerebellum; asterisk = granular layer; avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×200 c) Severe suppurative encephalitis in the cerebellar white matter; asterisk = granular layer; hematoxylin–eosin, magnification ×200; d) Demonstration of intralesional *Listeria monocytogenes* antigen by immunohistochemistry; asterisk = granular layer; avidin–biotin–peroxidase complex method; hematoxylin counterstain; magnification ×400.

Distemper-like diseases in dolphins and harbor porpoises are caused by the dolphin morbillivirus (DMV) and porpoise morbillivirus (PMV), respectively [145]. Together with the pilot whale morbillivirus, isolated from a stranded long-finned pilot whale (*Globicephalus melas*), DMV and PMV are members of the cetacean morbillivirus group [145]. Analysis revealed that these cetacean viruses are more closely related to rinderpest virus and *peste-des-petits*-ruminants virus than to CDV [146]. Viruses isolated from Mediterranean monk seals (*Monachus monachus*) during mass die-offs closely resemble cetacean morbilliviruses, indicative of interspecies transmission from cetaceans to pinnipeds [147,148]

wildlife species, but also spillback events from wildlife reservoir hosts to domesticated animals occur [149]. Epidemiology of distemper in wildlife animals depends upon several factors, such as virulence of virus strain, population density, and herd immunity [3,9]. Also genetic diversity of CDV strains represents a possible cause for unpredictable disease emergence in domestic and wildlife populations [127,150]. Thus, in contrast to host-specific pathogens, such as measles virus and rinderpest virus, the broad and expanding host range of CDV considerably hampers disease eradication even by widespread mass vaccination [105,151,152].

Conclusion

Spillover of CDV resulting from interactions between domestic or feral dogs and various wild species has led to mass mortalities in several
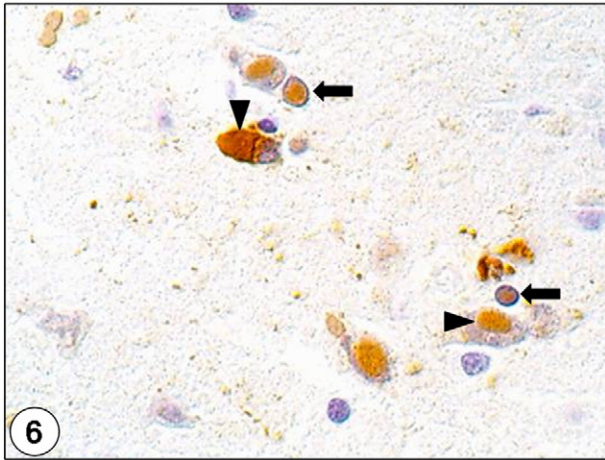
Acknowledgment

Fig. 6. Canine distemper virus infection in a spotted hyena from the Serengeti National Park; demonstration of viral antigen in nuclei (arrows) and cytoplasm (arrowheads) of neuronal and glial cells of the brain by immunohistochemistry. Peroxidase-antiperoxidase technique; hematoxylin counterstain; magnification ×600.

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