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CHAPTER

15

Viral Diseases of Common Marmosets

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HERPESVIRUSES

Etiology. The family Herpesviridae is divided into the three subfamilies of *Alpha-, Beta-, and Gammaherpesvirinae*. Members of the family Herpesviridae are typical DNA viruses with a complex double-stranded DNA genome embedded in an icosahedral capsid. They are well adapted to their natural hosts and are able to persist in a latent form within their hosts. Some have the potential to cross species barriers and can induce severe zoonotic infections in susceptible species. For common marmosets, the most important herpesviruses are the *Herpes simplex virus* of the *Alphaherpesvirinae* subfamily and the *Callitrichine herpesvirus 3*, a recently recognized lymphocryptovirus of the *Gammaherpesvirinae* subfamily.

Herpes Simplex Virus

Clinical signs. Marmosets are highly susceptible hosts to human *Herpes simplex virus* (HSV-1,2) [1]. Humans are the original host and the reservoir for HSV. In its natural host, HSV-1 and 2 cause only mild facial lesions, including gingivostomatitis or keratitis, or lead to clinically inapparent infections. There is lifelong infection with *Herpes simplex virus* because of viral latency in sensory neurons. Only in neonates or immunocompromised individuals, fatal encephalitis or systemic disease can occur. When immunity is compromised by stress or disease, the virus becomes activated by suppression of the latency-associated transcript gene. At this stage, the virus can be shed even in the absence of visible lesions. Oral, conjunctival infection and meningoencephalitis are most commonly caused by HSV-1, whereas genital and neonatal infection is usually attributed to HSV-2 infection. Primates are susceptible to both serotypes. Transmission occurs from humans to monkeys and vice versa, leading to epizootics with high morbidity and mortality in common marmosets. There is no evidence for the presence of HSV-1,2 genotypes exhibiting a higher virulence for animals [2]. Spontaneous HSV-1 infections are described in wild marmosets (black tufted-ear marmosets, *Callithrix penicillata*) in a natural park in Brazil [3,4], in young pet marmosets (*Callithrix jacchus*) in private husbandries [5–8], and in a semifree-living common marmoset colony in Germany [9]. Most reported cases of herpesvirus infection in callitrichids occurred in animals kept privately, often in close association with the family.

Epizootiology. The most likely source of transmission is direct close contact to humans suffering from oral herpesvirus infection. The disease is spread by contact with infected saliva or via contaminated objects. Animal owners, visitors, students, or caretakers might be able to infect the animals accidentally, for example, by passing partly eaten food into the cages or by practicing mouth-to-mouth feeding of hand-raised offspring [5]. Once brought into a colony, the disease is spread rapidly between the animals by direct contact and by aerogenous transmission.

Pathology. Usually, infection leads to a severe, rapidly progressing and often fatal generalized febrile disease with typical lesions on oral mucous membranes [1,7]. Clinical symptoms depend on the extent and severity of gross alterations. Infected animals show severe apathy, anorexia, weakness, and marked salivation or serous nasal discharge before they become moribund and die [9]. Death occurs within 2–14 days after the onset of the first symptoms. In rare cases, infected animals survive and develop a persistent infection, which can be monitored by serologic examination [5]. Gross pathology is characterized by erosions and ulcers of variable extent on oral or genital mucous membranes and mucocutaneous junctions of the lips, which may become confluent and are covered by a fibrinonecrotic exudate (Fig. 15.1). The lesions are accompanied by severe lymphadenopathy of regional lymph nodes. Areas of necrosis and hemorrhage may be present in other organ

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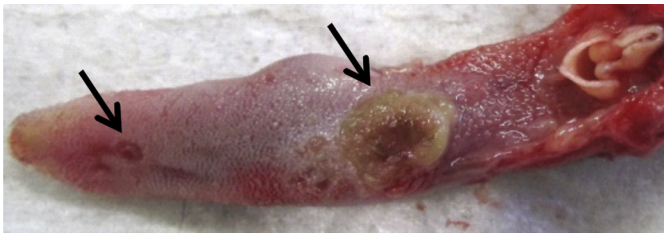

FIGURE 15.1 Common marmoset, tongue, naturally acquired *Herpes simplex virus* infection. Tongue with multifocal to confluent ulcerations (*arrows*).

systems if the disease disseminates. In severe cases, the cerebral cortex may also be involved [5,7]. Histopathologic changes consist of severe vesiculation and ulceration of squamous epithelia of mucous membranes and tongue with acantholysis, parakeratosis, coagulation necrosis, and polykaryocytosis. Necrotic foci may extend from the submucosa to the surface epithelium (Fig. 15.2A). Epithelial cells at the ulcer margins show varying degrees of degeneration and necrosis. Typical intranuclear inclusion bodies are key morphologic features of HSV infection. They are commonly found in epithelial cells at the borders of vesicles and ulcers. These intranuclear inclusions are surrounded by a clear halo and appear red-blue in Feulgen-stained sections. The presence of HSV antigen can be confirmed by immunohistochemistry using commercial antibodies against *Herpes simplex* antigen. Nonsuppurative meningoencephalitis is a frequent finding in HSV-infected callitrichids [5] (Fig. 15.2B). In cases with meningoencephalitis, intranuclear inclusion bodies can be found within neurons and glial cells. The widespread distribution of the virus within neurons and glia cells can be demonstrated by immunohistochemistry (Fig. 15.2C). Using transmission electron microscopy, large numbers of enveloped virions can usually be detected in the cytoplasm and within intercellular spaces (Fig. 15.2D). Intranuclear particles measure 80–100 nm, the enveloped extranuclear particles have an outside diameter of 150 mm or more. Similar gross and histologic lesions are observed in experimentally infected marmosets [10].

Diagnosis. Diagnosis is based on histologic, immunohistologic, and electron microscopic findings, with demonstration of classic intranuclear inclusion bodies. Commercial antibodies used for HSV detection by

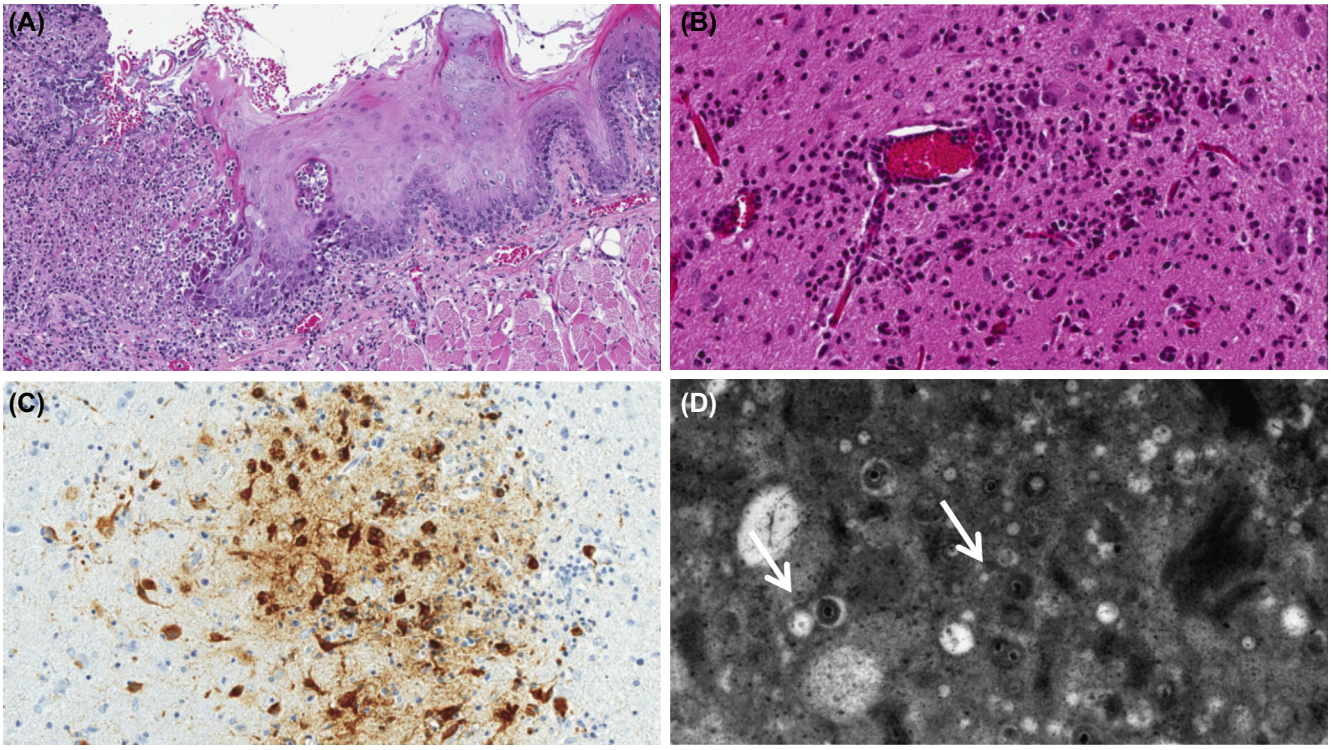

FIGURE 15.2 (A–D) Common marmoset with naturally acquired *Herpes simplex virus* infection. (A) Tongue, severe ulceration and necrosis of the epithelium. Intranuclear inclusion bodies are present in epithelial cells at the ulcer margin, paraffin section stained with hematoxylin-eosin (HE). (B) Moderate nonsuppurative meningoencephalitis with perivascular mononuclear cuffing, paraffin section stained with HE. (C) Widespread evidence of *Herpes simplex* antigen within infected neurons, immunohistochemistry on paraffin sections. (D) Transmission electron microscopy of the ulcerative epithelial lesions reveals the presence of large numbers of enveloped virions with typical herpes morphology (*arrows*).

immunohistochemistry are cross-reactive to other members of the simplexvirus genus. Therefore, definitive diagnosis requires virus isolation and detection of viral sequences using molecular assays.

Prevention and control. Treatment protocols are not available, but application of antiviral drugs in early stages of the disease might be beneficial. Because humans are the natural or reservoir host of the virus, contact with symptomatically and subclinically HSV-1-infected humans should always be avoided. Infected persons can excrete the virus even in the absence of visible lesions. The use of appropriate personal protective clothing and face masks is required.

Saimiriine Herpesvirus 1

Etiology. *Saimiriine herpesvirus 1* (SaHV1), previously known as *Herpesvirus tamarinus* or *Herpes T*, is an alpha herpesvirus, which induces an infection with many similarities to *Herpes simplex virus* infection in New World monkeys. Reservoir hosts are squirrel monkeys, which are naturally infected [11].

Clinical signs. Squirrel monkeys harbor the virus without developing clinical disease. In rare cases, mild oral ulceration indicates SaHV1 infection. Persistence of the virus within sensory ganglia has been documented. The virus may be shed during periods of reactivation with oral secretions. Marmosets and tamarins are highly susceptible to SaHV1 and may develop an acute lethal disease. After an incubation period of 7–10 days, exposed animals show signs of a disseminated infection with necrotizing inflammation in various organs. Clinical signs are vesiculation and ulceration of skin and oral mucous membranes.

Pathology. In addition to vesiculation and ulceration of skin and oral mucous membranes, further gross findings include ulceration and hemorrhage throughout the alimentary tract. Histologically, initial intraepidermal vesicles in the skin progress to full-thickness necrosis. Adnexal structures such as sebaceous glands and hair follicles are spared. Multinucleated giant cells may be present and reveal intranuclear inclusion bodies. Necrotizing inflammation is further noted in liver, spleen, kidney, adrenal gland, and lung. In contrast to *Herpes simplex virus* infection, meningoencephalitis is only minimal [12]. Nevertheless, meningoencephalitis is not a criterion to distinguish between both herpesvirus infections.

Prevention and control. Prevention requires separation of susceptible callitrichids from reservoir hosts such as *Saimiri*, *Ateles*, *Cebus*, and *Lagothrix*. In the past, a live vaccine has been developed, but vaccination frequently failed and vaccinated animals developed vaccine-induced diseases [13].

Cytomegalovirus

Simian cytomegaloviruses (CMVs) are described in a variety of New World and Old World monkey species. CMVs generally have a restricted host range, and infection of the healthy mature host is usually asymptomatic. CMVs are typical opportunistic agents, and infection and disease become apparent only in immunodeficient individuals. Two marmoset CMVs, *Callitrichine herpesvirus 1 and 2*, are known, which are not associated with disease [12].

Lymphocryptovirus

Etiology. Nonhuman primates are naturally infected with species-specific gamma herpesviruses belonging to the genus *Lymphocryptovirus*. More than 50 distinct simian lymphocryptoviruses have been isolated [14]. All lymphocryptoviruses are closely related to *Human herpesvirus 4*, the *Epstein–Barr virus* (EBV). EBV infects B lymphocytes and is indigenous to humans. Infected humans develop lifelong latent infections and most cases remain asymptomatic. Under certain conditions, the virus can cause infectious mononucleosis. Furthermore, there is an association between infection and tumor development. In this context, EBV is involved in the pathogenesis of Burkitt's lymphoma, T-cell lymphoma, and nasopharyngeal carcinoma, as well as in oral hairy leukoplacia and non-Hodgkin's lymphoma in immunocompromised patients. In general, infection is not associated with disease in the natural host. Immunosuppression of latently infected individuals or infection of nonnatural hosts may lead to rapid lymphoproliferation or lymphomatous disease. Spontaneous disease attributed to EBV infection in common marmosets is not reported, but the demonstration of serum antibodies against EBV indicates that marmosets are susceptible hosts. Experimental EBV infection of common marmosets leads to seroconversion, but there is no definite evidence of lymphoproliferative disease or lymphoma [15].

Epizootiology. Infected animals become positive for early antigen, virus capsid antigen, and nuclear antigen at low levels and show an increase in the number of leukocytes [16]. Their responses to experimental EBV infection partly resemble those of humans, and common marmosets may provide a useful model for exploring the potential of cofactors involved in the development of EBV-associated neoplasia [17]. Cotton-top tamarins (*Saguinus oedipus*) experimentally infected with EBV B95-8 virus react in a different manner and develop a fatal lymphoproliferative disease that resembles human Burkitt's lymphoma [18,19]. Similarly, white-lipped marmosets (*Saguinus labiatus*) develop lymphoma following experimental EBV inoculation [20].

Callitrichine Herpesvirus 3

Etiology. Common marmosets are frequently infected with marmoset lymphocryptovirus or *Callitrichine herpesvirus 3* (CalHV3), which was first identified in 2000. The virus may induce lymphoproliferative disease and B-cell lymphoma of the intestinal tract and associated lymph nodes [21,22], but the causative role and oncogenic potential of this virus are not definitive proof. Several outbreaks and individual cases of CalHV3 infection have been documented in zoo and laboratory settings. CalHV3 is a typical lymphocryptovirus with a complex genome that is now completely sequenced. The sequence demonstrates on overall homology with the EBV genome of 43% suggesting that CalHV3 is more closely related to a primitive lymphocryptovirus, from which all other lymphocryptoviruses evolved [23].

Epizootiology. Almost 35%–65% of wild-caught and captive marmosets are seropositive for the virus. The seroprevalence of marmoset lymphocryptovirus infection is not as ubiquitous as infection with EBV in humans or lymphocryptovirus infection in Old World monkeys, in which a prevalence of 100% among adults can be assumed [24]. Most infected marmosets do not show overt signs of clinical disease. Rarely, affected animals develop weight loss, inappetence, and diarrhea.

Pathology. Intestinal obstruction due to intraabdominal masses may occur. Most frequently, the hemogram is nonspecific, although neutrophilia with left shift and elevated liver enzymes may be present. Gross pathology reveals enlarged mesenteric lymph nodes. The digestive tract is frequently dilated, and the mucosa is thickened. Histologically, lymph node architecture is completely obliterated by sheets of infiltrating heterogeneous neoplastic round cells identified as B lymphocytes by immunohistochemistry. Small amounts of reactive T lymphocytes are scattered among neoplastic cells. Similar infiltrates can be found in the colonic mucosa, infiltrating and expanding the lamina propria and less frequently the submucosa, muscularis, and serosa. The mucosa of the small intestine may be similarly altered (Fig. 15.3). Neoplastic cellular infiltrates may also occur in liver, kidney, and lung [22]. The development of spontaneous CalHV3-positive lymphosarcomas in otherwise healthy and immunocompetent marmosets suggests that other cofactors contribute to CalHV3-associated lymphomagenesis [21]. A causative role of CalHV3 in the development of other gastrointestinal tumors, like carcinomas as observed in humans, seems unlikely in this species [25].

Diagnosis, prevention, and control. Serologic tests are available to diagnose animals with latent infections. This offers the possibility to identify and isolate infected animals and build up colonies that are free of this herpesvirus. There is no known zoonotic potential.

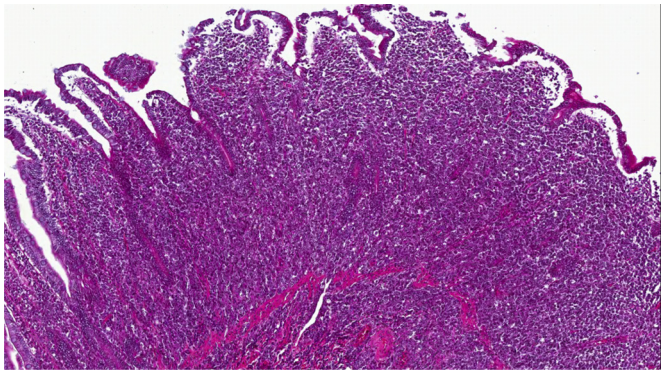

FIGURE 15.3 Common marmoset with natural *Callitrichine herpesvirus 3* infection. The small intestinal mucosa is infiltrated by a heterogenous neoplastic round cell population, paraffin section stained with HE.

Saimiriine Herpesvirus 2

Etiology. *Saimiriine herpesvirus 2*, also known as *Herpesvirus saimiri* (HVS), is a gamma herpesvirus closely related to the *Kaposi's sarcoma-associated herpesvirus* (HHV-8) of humans. The T-lymphotropic virus is naturally found in squirrel monkeys (*Saimiri sciureus*), in which it does not cause disease [26]. Virtually all squirrel monkeys are persistently infected with HVS. Transmission is horizontal, and the infection is acquired via saliva in the first 2 years of life [27]. The virus infects T lymphocytes and persists within sensory ganglia. Infected T lymphocytes are transformed into neoplastic cells by the oncogenic properties of the virus.

Clinical signs. There is no disease in the natural host, but experimental transmission of HVS to common marmosets and other susceptible New World monkeys leads to a fatal acute lymphoproliferative disorder [28]. The clinical outcome of experimental infections largely depends on the virus strain. Three different subgroups of HVA (A, B, and C) are discriminated on the basis of DNA sequence divergence at the left terminus of L-DNA [29]. Subtypes A and C are highly oncogenic, transforming marmoset peripheral blood lymphocytes in vitro and inducing rapidly progressing T-cell lymphomas in a variety of New World primate species [30]. After experimental infection, different disease patterns occur depending on virus strain and host. The time span from infection to lymphoma development may be as short as 3 weeks with a mean survival time of 22–42 days [31,32]. Animals that survive less than 40 days develop aggressive disseminated lymphomas associated with extensive necrosis and replacement of normal tissue structure. Longer survival times are associated with less progressive lymphoma development and/or leukemia.

Pathology. Gross pathology is characterized by severely enlarged peripheral and visceral lymph nodes

and splenomegaly. Other characteristic lesions include enlarged and hemorrhagic thymuses, tonsils, and Peyer's patches. The basic histologic lesions are disseminated lymphoblastic infiltrates in almost every organ [33]. The cells are arranged in discrete nodules or, more frequently, in sheets of neoplastic cells exhibiting infiltrative and invasive growth. Neoplastic cells are pleomorphic and round with two large nucleoli in most cells. Leukemia is infrequently present. The neoplastic cells are of T-cell origin.

Prevention and control. HVS is primarily an experimental disease. Accidental natural transmission from squirrel monkeys to callitrichids in zoos is possible. Therefore, squirrel monkeys should not be kept in mixed enclosures together with marmosets and tamarins. There is no known zoonotic potential.

Ateline Herpesvirus

Ateline herpesvirus (AtHV) 2,3 or *Herpesvirus ateles* is another gamma herpesvirus closely related to HVS [34]. The virus is naturally found in spider monkeys (*Ateles* spp.), in which it does not lead to clinical disease. AtHV has similar pathogenic properties as *Herpesvirus saimiri* in other New World primate species. The survival time after experimental infection ranges from 36 to 104 days and is extended when compared with HVS. The lesions induced by both viruses are almost identical [31,35].

POXVIRUSES

Etiology. Poxviruses are large, brick- to ovoid-shaped enveloped DNA viruses. Different members of the *Orthopoxvirus* (OPV) family may infect callitrichids, but infections with members of the genus *Yatapox virus*, including *Yaba monkey tumor virus* and *Yaba-like disease virus*, are not reported to occur among New World monkeys. The most important pathogen among the OPVs is the *Variola virus* (VARV), the causative agent of smallpox, which only naturally infects humans. In contrast, *Vaccinia virus* (VACV) and *Cowpox virus* (CPXV) have a broad host range and are able to infect humans, cattle, cats, rodents, and nonhuman primates. *Vaccinia virus* is a live attenuated orthopoxvirus used in smallpox vaccination programs. Modified Vaccinia virus Ankara (MVA) or Vaccinia virus Lister-Elstree (VACV LE-BN) are classical vaccines used in the smallpox eradication campaigns. MVA is frequently used in different nonhuman primate animal models as a vector for recombinant vaccines. In common marmosets, a typical "vaccine take" arises at the injection site following intradermal injection of VACV LE-BN with the multipuncture method using standard bifurcated needles (Fig. 15.4). A focal poxlike skin lesion develops between days 4 and 28, and the animals remain infectious after vaccination until the skin lesions are completely healed. In vaccinated marmosets, OPV-specific IgM and IgG antibodies are observed between day 11 and day 21 after vaccination. Neutralizing antibodies start rising from day 21 postvaccination onward (own observations).

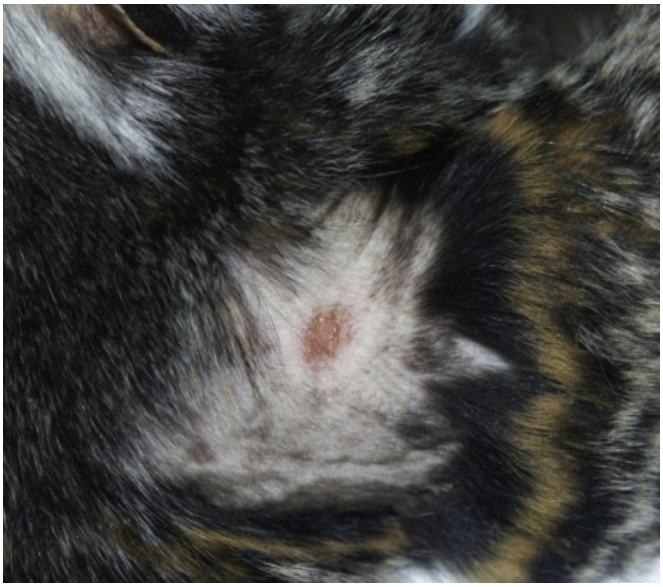

FIGURE 15.4 Common marmoset, skin. Intradermal inoculation of *Vaccinia virus* Lister-Elstree induces a typical pox lesion (vaccine-take) in the skin.

Cowpox Virus

Epizoology. Callitrichids, especially common marmosets, are highly susceptible to *Cowpox virus* (CPXV), another orthopoxvirus that is endemic in rodents. The virus seems to be limited to Europe and Central Asia and is endemic in wild rodents such as bank voles (*Clethrionomys glareolus*), wood mice (*Apodemus sylvaticus*), and rats (*Rattus norvegicus*) [36,37], which serve as vectors. Domestic cats can become infected by contact with infected rodents and are potential vectors responsible for the majority of human CPXV infections [38]. CPXV has also been isolated from a variety of zoo animals including Old World monkeys [39–41].

Clinical signs. Normally, infection is acquired through skin lesions resulting in a local often self-limiting infection at the site of inoculation. A generalized infection with severe often fatal clinical disease can occur in immunodeficient individuals or highly susceptible species. It seems that cowpox infections occur as sporadic outbreaks depending on environmental viral burden and the pathogenetic potential of the virus. In common marmosets, natural and experimental infection

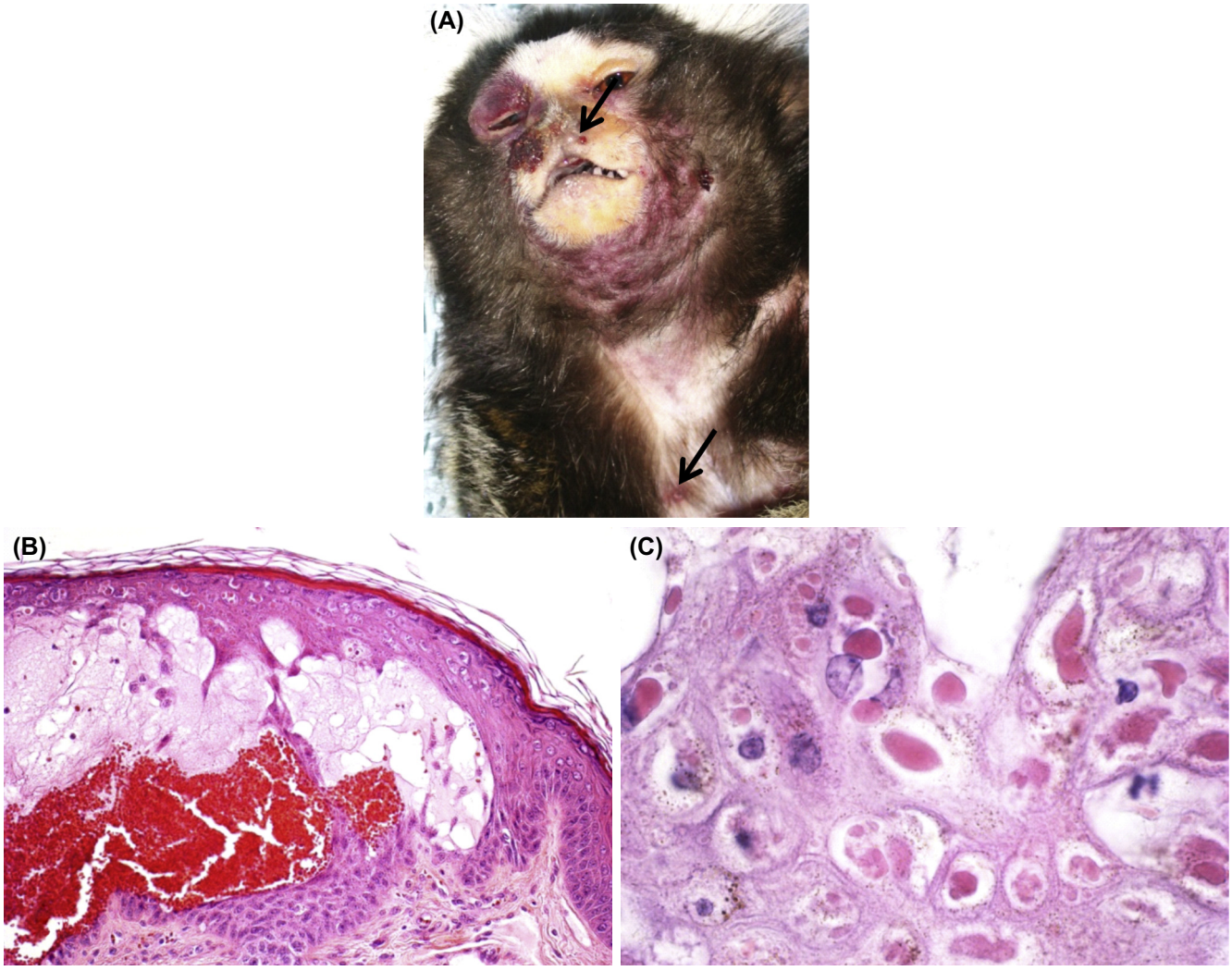

FIGURE 15.5 (A–C) Common marmoset, skin, experimental infection with a New World monkey-adapted cowpox virus named calpox virus, which closely mimics the natural disease. (A) Severe cutaneous edema and hemorrhages and vesicular lesions of different extent around the nose covered by serocellular crusts. More vesicles are randomly distributed on the body skin (*arrow*). (B) Severe focal vesicular dermatitis with intraepidermal hemorrhages, acantholysis, acanthosis, and syncytia formation of basal keratinocytes, paraffin section stained with HE. (C) Accumulation of large Guarnieri bodies in altered epithelial cells, paraffin section stained with HE.

leads to severe vesicular, hemorrhagic dermal lesions, preferentially in the facial skin (Fig. 15.5A), scrotum/labia, and palmar or plantar surfaces. For modeling orthopoxvirus infection, a New World monkey-adapted cowpox virus named calpox virus is used, which was isolated during a natural disease outbreak [42]. Experimentally induced disease is similar to the natural infection [43].

Pathology. Histologically, vesicular skin lesions show acanthosis, vesiculation, hemorrhage, and necrosis with typical orthopoxvirus inclusion bodies (Guanieri bodies) in epithelial cells and syncytia formation of the basal keratinocytes (Fig. 15.5B andC). Lymph nodes are hyperplastic and reveal hemorrhages and necrosis, which are also infrequently found in other organs, especially lung, liver, and spleen. The disease course in marmosets is fatal [41–43]. Similar alterations have been described in common marmosets during an earlier outbreak that was originally attributed to *Yatapoxvirus* [44].

Diagnosis. Diagnosis is based on typical histologic and electron microscopic findings, virus isolation, and molecular biologic identification.

Prevention and control. Cowpox virus infections are zoonotic diseases, and infected animals should be handled with care. Vaccination with modified vaccinia virus Ankara (MVA) or vaccinia virus Lister-Elstree (VACV LE-BN) is protective.

ORTHOMYXOVIRUSES

Etiology. Influenza virus is an enveloped single-stranded RNA virus in the family Orthomyxoviridae. Influenza A viruses are classified according to subtypes based on two surface proteins (hemagglutinin [H] and neuraminidase [N]) [45]. Natural infection of common marmosets with influenza A virus has not been described, but the marmoset is susceptible to experimental infection with pandemic H1N1 influenza virus strains (influenza A/Mexico/InDRE4487/2009 and influenza A/California/07/2009) [46,47]. Animal-to-animal transmission has been demonstrated at least for the influenza A/California/07/2009 virus strain [46]. Infected marmosets develop human-like "flu" symptoms between 5 and 8 days after exposure, including nasal discharge, sneezing, labored breathing, and loss of appetite [46,47]. Total protein levels are elevated in bronchoalveolar lavage fluid of infected animals between days 9 and 27 after exposure, indicating lung damage [46]. Gross pulmonary lesions of marmosets include multifocal hemorrhage, edema, and consolidation [47]. A detailed description of the microscopic lesions in common marmosets is not available.

ADENOVIRUSES

Etiology. Adenoviruses isolated from NHP belong to the genus *Mastadenovirus* in the family Adenoviridae. Adenoviruses are nonenveloped, double-stranded DNA viruses that are associated with mild to moderate respiratory or enteric disease in monkeys and apes. However, many isolates have been obtained from swabs or cell culture derived from clinically healthy animals indicating that subclinical or persistent infections are common in NHP species [12].

Clinical signs. Clinical disease due to natural adenovirus infection is not documented in common marmosets, but evidence of latent infection is supported by the observation of neutralizing antibodies to human and chimpanzee adenovirus serotypes [48] and the detection of adenovirus sequences in liver tissue of captive common marmosets from Central Europe [49]. Experimental infection of common marmosets with *titi monkey adenovirus* (TMAdV), a novel adenovirus previously associated with acute respiratory illness in humans and rapidly fatal hepatitis and pneumonia in titi monkeys [50], leads to a productive infection with the onset of clinical symptoms at days 5–10 after intranasal inoculation, specific neutralizing antibody responses, and detection of the virus in nasal swabs up to 2 weeks postinoculation.

Pathology. Pathological lesions are limited to mild bronchitis, atypical nodular hyperplasia of the liver, and mild enterocolitis. Typical basophilic intranuclear inclusions consistent with active adenovirus infection were not observed in tissues from TMAdV-infected marmosets [51].

Diagnosis. Diagnosis is based on typical histologic and electron microscopic findings, virus isolation, and molecular biologic identification.

Prevention and control. Adenovirus should be considered as a zoonotic agent as there is evidence for cross-species transmission [49,51,52], and infected animals should be handled with care. Wearing protective clothing and face masks when handling marmosets may minimize the risk of transmission.

CORONAVIRUSES

Etiology. Coronaviruses with relevance for NHPs belong to the genus *Betacoronavirus* within the family Coronaviridae. Common marmosets experimentally infected with *severe acute respiratory syndrome coronavirus* (SARS-CoV) and *Middle East respiratory syndrome coronavirus* (MERS-CoV) develop a disease similar to humans and represent a useful animal model for these highly pathogenic coronavirus species. Intratracheal inoculation of marmosets with SARS-CoV (Urbani strain) is associated with mild clinical disease, including an increase in rectal temperature, watery diarrhea, and dyspnea at 4 and 7 days after infection. Grossly, multifocal areas of pulmonary atelectasis and consolidation as well as tracheobronchial lymphadenopathy may be noted. The predominant histological lesion is a multifocal to coalescing interstitial pneumonia with multinucleated syncytial cells, type 2 pneumocyte hyperplasia, edema, and lymphocytic bronchiolitis. Tracheobronchial lymph nodes show parafollicular lymphocytic hyperplasia and histiocytosis within the subcapsular sinuses. Extrapulmonary findings include lymphocytic hepatitis with single cell necrosis, mild diffuse colitis, and mild multifocal lymphocytic myocarditis [53–55]. Common marmosets inoculated with a MERS-CoV strain (HCoV-EMC/2012) develop moderate to severe signs of respiratory disease, including increased respiratory rates, open-mouth breathing, anorexia, decreased levels of activity, and the presence of oral frothy hemorrhagic discharge. A transient decrease in body temperature may also be noted. Radiographic imaging of the lungs shows mild-to-severe bilateral interstitial infiltration. Major gross lesions are multifocal consolidation and dark red discoloration of the lungs. Microscopically, the lungs show multifocal to coalescing, moderate-to-severe

acute bronchointerstitial pneumonia, coupled with type 2 pneumocyte hyperplasia and consolidation of pulmonary fibrin [56,57]. Coronavirus-like particles have been detected by electron microscopy in feces of common marmosets and seem to be related to enterocolitis. Particles are characterized by regularly spaced petal-shaped projections from the surface and measure between 100 and 220 nm [58].

Both SARS and MERS are confirmed zoonotic diseases [59].

PARAMYXOVIRUSES

Etiology. Among the single-stranded RNA virus family Paramyxoviridae, parainfluenza virus 1 has previously been associated with epizootics of respiratory disease in common marmosets [60–63]. Infections with parainfluenza I virus result from direct contact or inhalation of aerosols and likely represent anthropozoonoses under conditions of crowding and stress. Clinical disease varies from mild upper respiratory tract disease to severe systemic illness and death and may be more severe in infant animals [61].

Clinical signs. Clinical symptoms include sneezing, ocular and nasal serous or purulent discharge, dyspnea, depression, and anorexia.

Pathology. Gross lesions consist of congestion and/or consolidation of the lungs and alveolar edema [63]. The main histological finding is an acute interstitial pneumonia of variable degree with evidence of multinucleated syncytial cells containing intranuclear and intracytoplasmic inclusion bodies [60,61]. Diagnostic tests include direct electron microscopy of nasal swab and lung specimens, immunofluorescence on lung tissue, and serological detection of neutralizing antibodies [60,61,63].

Prevention and control. As natural infection is usually self-limiting, treatment is largely symptomatic and is aimed to prevent secondary bacterial infections. Vaccines against parainfluenza are not available for NHPs [61]. Wearing protective clothing and face masks when handling marmosets may minimize the risk of transmission from humans.

Measles Virus

Etiology. Measles virus, a morbillivirus of the Paramyxoviridae family, may cause serious epizootics with high morbidity and mortality in marmoset species [61,64]. Measles virus is rapidly spread between animals through contact, fomites, and aerosols, and humans are regarded as the main source of infection [61,65,66]. Measles in NWM exhibit an inconsistent organotropism, whereas in OWM infected with measles virus, the respiratory tract and skin are the common sites of disease manifestation.

Clinical signs. While in mustached marmosets and several other NWM monkey species, the virus frequently targets the gastrointestinal tract and causes a necrotizing enterocolitis with hemorrhagic diarrhea [61,65], the predominant finding in naturally infected common marmosets is the characteristic pneumonia [64,67]. Common marmosets with measles infection become clinically apparent with lethargy, facial edema, and nasal discharge and occasionally develop an exanthema. Death occurs 8–18 h after the onset of the first clinical signs.

Pathology. The characteristic histopathological finding is an interstitial pneumonia with thickened and hyperemic alveolar walls. Syncytial epithelial cells containing eosinophilic intracytoplasmic or intranuclear inclusion bodies are the hallmark of the disease but are not an obligatory finding and are often absent in the skin lesions [64,67]. Secondary bacterial infection occasionally results in patchy bronchopneumonia. Multinucleated syncytial cells with or without inclusion bodies may be found in different organs, including lymph nodes (Warthin–Finkeldey cells), spleen, and colon. The maculopapular skin lesions are histologically characterized by focal hyperemia and hemorrhages in the lamina propria [64]. Experimental intracerebral inoculation of marmosets may cause encephalitis, which is similar to the subacute, sclerosing panencephalitis in humans [67,68]. Measles virus is strongly immunosuppressive, and the clinical picture may be complicated by secondary opportunistic viral or bacterial infections [67].

Diagnosis. Diagnostic tools to confirm measles virus etiology include detection of seroconversion, virus isolation, or immunohistochemical demonstration of viral antigen in tissue sections. Treatment of measles is limited to supportive therapy with fluids and antibiotics to prevent secondary bacterial infections [61].

Prevention and control. Experiences with efficacy and tolerability of commercial vaccines in common marmosets are not reported in the literature. Measles constitutes a zoonotic risk for naive humans [61], and protective clothing and face masks should be used when handling potentially infected marmosets.

Paramyxovirus Saguinus

Etiology. *Paramyxovirus saguinus*, which presumably is a variant of measles virus, is associated with a single outbreak of infectious gastroenteritis in a marmoset

colony at the New England Primate Research Center [69]. The virus is described to infect cotton-top tamarins, mustached tamarins, and common marmosets and causes clinical symptoms such as anorexia, diarrhea, and dehydration with rapid progression to death. Gross lesions include congestion and hemorrhage of the gastrointestinal mucosa and enlargement of lymphoid tissues (Peyer's patches, lymph nodes, spleen). The predominant microscopic lesion is a necrotizing and ulcerative typhlocolitis with evidence of multinucleated syncytial cells on the surface epithelium and within crypts. Intranuclear and/or intracytoplasmic inclusions can occasionally be observed in the multinucleated cells. Syncytial cells may also be present in bile and pancreatic duct epithelium, pancreatic acini, hepatic cords, kidney tubules, and in endometrial epithelium. Further histologic findings include cholangitis and necrosis of germinal centers in lymph nodes, spleen, and Peyer's patches [69]. The virus is most likely transmitted via the fecal–oral route. The origin of infection remains unknown. Preventive or curative treatment is not available.

CALLITRICHID HEPATITIS VIRUS

Etiology. Callitrichid hepatitis is an acute fatal infection of New World primates caused by an arenavirus referred to as callitrichid hepatitis virus. The virus is an enveloped RNA virus closely related to lymphocytic choriomeningitis virus (LCMV) [70], for which the house mouse (*Mus musculus*) is the major reservoir. LCMV can cause human disease characterized by mostly self-limiting influenza-like illness, but the disease can progress to acute meningitis. Several outbreaks of hepatitis among captive callitrichids are reported in the United States, which are frequently related to feeding of neonatal mice infected with LCMV [71–73]. The first outbreak in Germany was mostly attributed to transmission by wild mice [74]. In general, transmission occurs through contact with or ingestion of infected rodents.

Clinical signs. Clinical signs include dyspnea, weakness, and jaundice. Serum levels of transaminases and bilirubin are elevated. Infected animals die 7–12 days after the onset of clinical symptoms. Coagulopathy may be apparent.

Pathology. At necropsy, hepatosplenomegaly, pleural and pericardial effusions, jaundice, and subcutaneous and intramuscular hemorrhages are characteristic [72]. Histopathologically, random foci of hepatocellular degeneration and spotty necrosis associated with mononuclear inflammatory cell infiltration occur throughout the liver. LCMV antigen is usually demonstrable within these foci. Round acidophilic structures resembling apoptotic or Councilman-like bodies are commonly present (Fig. 15.6A). They are located free within sinusoids or within Kupffer cells. Necrotic lesions also occur in other organs such as the spleen, lymph nodes, adrenal cortex, and intestine. Nonsuppurative meningitis and encephalitis may accompany the liver lesions (Fig. 15.6B). These extrahepatic lesions are usually milder than the liver alterations [71]. Electron microscopy may reveal enveloped virus-like particles with a diameter of 85–105 nm in the rough endoplasmic reticulum and Golgi complex of hepatocytes. Experimental infection of marmosets is possible and leads to identical clinical and pathological findings [71,75].

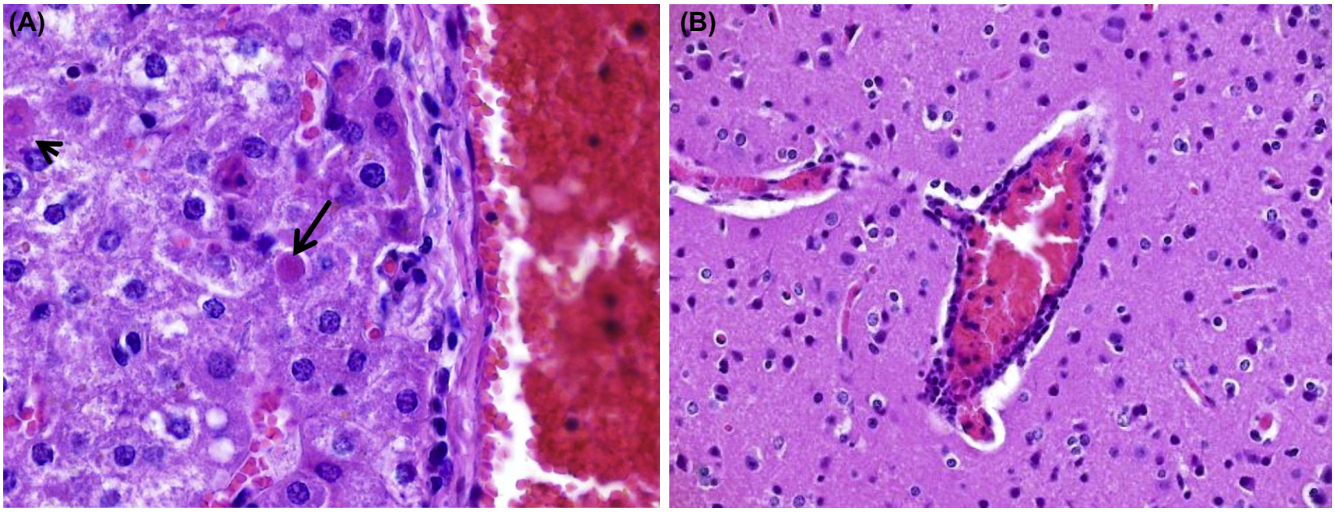

FIGURE 15.6 (A and B) Emperor tamarin (*Saguinus imperator*) with naturally acquired LCMV infection. (A) Liver, hepatocellular degeneration and necrosis with intracytoplasmatic inclusion bodies (*arrows*) and Councilman bodies (*short arrow*), paraffin section stained with HE. (B) Central nervous system, mild encephalitis with perivascular cuffing, paraffin section stained with HE.

Prevention and control. Preventing contact with rodents is essential to avoid this rodent-borne disease. LCMV is a zoonotic agent and may cause disease in humans. Seroconversion is documented in caretakers involved in outbreaks of the disease [71].

HEPATITIS A VIRUS

Etiology. Hepatitis A virus (HAV) is a major cause of acute viral hepatitis in humans and several nonhuman primate species. Common marmosets can also be infected as indicated by serologic surveys [76,77]. The virus is a small RNA virus and belongs to the genus *Hepatovirus* within the family Picornaviridae. Transmission occurs by the fecal–oral route.

Clinical signs. Clinical findings are uncommon, and seroconversion and elevation of liver enzymes are usually the only clinical signs of infection. In the past, common marmosets have been used as an animal model for the disease. They can be infected by the oral route [78], via intragastric infection [79], or by direct inoculation of the virus in the liver [80]. Infected animals develop an acute hepatitis 2 weeks after infection and shed the virus in feces from day 7 onward.

Pathology. The liver is the target organ, and viral replication occurs within hepatocytes. Usually, HAV antigen is not detectable in other organs, indicating that the liver is the only and primary site of virus replication. Shedding of HAV in feces during the late incubation period can be explained by excretion of HAV from the liver with the bile [81]. The end of the incubation period is indicated by an initial increase in serum liver enzymes. Characteristic histopathologic changes such as activation of sinusoidal cells, piecemeal necrosis, and bridging necrosis as well as periportal and parenchymal mononuclear inflammatory cell infiltration are detectable during the acute phase, coinciding with a maximum of transaminase levels and the appearance of anti-HAV antibodies [79]. At the same time, clusters of solid or empty virus-like particles about 27 nm in diameter can be demonstrated by electron microscopy mainly in membrane-bound cytoplasmic vesicles of Kupffer cells and hepatocytes [82]. In the convalescent phase, regeneration of hepatic tissue starts and the transaminase values return to baseline. HAV is a potentially zoonotic agent; monkeys can become infected with human strains, but infection is usually self-limiting. Chronic infections and carrier stages are not described.

HEPATITIS B VIRUS

Etiology. The major cause of human hepatitis is the hepatitis B virus (HBV), which belongs to the genus *Orthohepadnavirus*. Transmission occurs by infected blood, saliva, and semen. HBV can cause persistent infections leading to chronic hepatitis and hepatocellular carcinomas. The virus can be transmitted to chimpanzees and macaques [83,84]. Natural infections among New World monkeys are not observed.

HEPATITIS C VIRUS

Etiology. Hepatitis C virus (HCV) is a small enveloped RNA virus that causes chronic hepatitis in humans worldwide. HCV is a member of the genus *Hepacivirus* within the family Flaviviridae. HCV is not associated with natural disease in nonhuman primates, and experimental infection of several nonhuman primate species failed. Only chimpanzees are susceptible and represent an important animal model for chronic hepatitis. In contrast, GB agent viruses are frequently found in a number of New World monkeys; GBV-A and variants are enzootic viral infections of several NWP species including common marmosets, whereas GBV-B and GBV-C are blood-borne pathogens of man and chimpanzees. GB agent viruses are closely related to HCV of humans. They are single-stranded, positive-sense RNA viruses belonging to the same genus and family as HCV. Several GBV-A variants seem to circulate in wild populations of New World monkeys. No clinical disease is associated with GBV-A and C infection, and diagnosis is confirmed using RT-PCR performed on plasma or serum. In contrast, GBV B can induce an acute hepatitis when inoculated intravenously into several species of New World primates. Common marmosets are susceptible to experimental GBV-B infection and develop a characteristic acute nonsuppurative hepatitis, which is characterized by an infiltration of lymphocytes, mainly CD3+ CD8+ T lymphocytes and CD20+ B lymphocytes, within the first 2 months of primary infection [85]. Experimental GBV-B infection of marmosets can be used as a surrogate model of HCV infection for investigation of pathogenetic pathways and antiviral drug development [86].

FLAVIVIRUSES

Etiology. Yellow fever induced by the yellow fever virus (YFV), another flavivirus belonging to the family Flaviviridae, is a devastating viral infection of free-living New World monkeys. The disease is transmitted by mosquitoes of the genera *Aedes* and *Haemagogus*, which serve as vectors. YFV is endemic in South America, and the disease naturally occurs among wild marmosets and tamarins [87]. Devastating outbreaks

are reported among howler monkeys. They frequently coincide with human cases in the geographic vicinity [88,89]. Suspected epizootics among common marmosets in endemic areas could not be confirmed [90]. Experimentally infected callitrichids rapidly succumb to disease, and death occurs within 1 week after infection. Gross lesions are not specific except for fever and jaundice, which are infrequently observed. Histologically, liver lesions are described, including hepatocellular necrosis, fatty change, and hemorrhage. Acidophilic apoptotic (Councilman) bodies are rarely observed [91,92]. As the disease is primarily a problem of wild living primates, it should be considered as a differential diagnosis in cases of hemorrhagic fever occurring in endemic regions or in recently imported monkeys originating from endemic areas. Experimental infection has shown that common marmosets are highly susceptible for other RNA viruses belonging to the Bunyaviridae, Arenaviridae, and Filoviridae families, all inducing hemorrhagic fevers. Common marmosets are used as animal models for Lassa fever induced by Arenaviridae, Argentine hemorrhagic fever induced by Junin virus, and filovirus hemorrhagic fever induced by Ebola and Marburg virus [53].

LYSSAVIRUS

Etiology. Rabies is caused by Lyssaviruses, belonging to the family Rhabdoviridae, encompassing a diverse group of viruses. Rabies is rarely considered as a cause of morbidity and mortality in nonhuman primates. Nevertheless, the disease has been reported in several New World monkey species, among them common marmosets [93]. In endemic regions, wild nonhuman primates may become infected in their natural habitat and represent important vectors of the virus. Several human cases could be traced back to contact with wild cuffed common marmosets raised as pets in a region of Brazil [94]. Here a marmoset-specific Rhabdovirus strain seems to exist.

Epizootiology. Nonhuman primates get infected by contact with reservoir or inadvertent host species such as dogs, bats, or rodents. The virus is spread by scratches or bites from animal to animal or from animal to human. Infection after vaccination with attenuated virus strains is reported [62]. The incubation time is not exactly known and can be long. Initial replication occurs at the site of inoculation followed by spread of the virus to the brain via the peripheral nerves. In the brain, the virus infects exclusively neurons and spreads rapidly. With the onset of clinical symptoms a widespread dissemination of the virus starts.

Clinical signs. Infection leads to disseminated meningoencephalitis inducing clinical furious or paralytic forms of the disease that result in self-mutilation, irritability, and paralysis. The disease can only be diagnosed after the start of symptoms. *Pathology* is characterized by nonsuppurative encephalitis with marked formation of glial nodules and neuronal degeneration. Eosinophilic intracytoplasmatic inclusions called Negri bodies within neurons are pathognomonic.

Diagnosis. The diagnosis is based on typical histologic findings, virus isolation, and molecular biologic identification. Diagnosis can be confirmed by the fluorescent antibody test using a rabies-specific antibody. *Differential diagnosis* in a case of suspected rabies should include any cause of encephalitis, in particular infection with herpesviruses, enteroviruses, or arboviruses.

Prevention and control. Rabies is a significant zoonotic threat, and suspected animals should be handled with care. A rabies vaccination can be included in the preventative health-care regimen. Vaccination of nonhuman primates housed in indoor/outdoor enclosures in rabies enzootic areas is advisable [95]. The use of attenuated vaccines should be avoided.

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