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Viral Infections of Rabbits

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KEYWORDS

• Borna disease virus • Caliciviridae infections • Coronavirus infections
• Herpesviridae infections • Papillomavirus infections • Poxviridae infections
• Rabbits • Rabies virus • Rotavirus infections

KEY POINTS

- Rabbit hemorrhagic disease is caused by a calicivirus and is characterized by fulminant hepatitis with a fatality rate of more than 90% in adult rabbits. It is not present in the United States. It is spread by direct contact between rabbits, by flies feeding on carcasses, and experimentally by fleas and mosquitoes. A single-dose vaccination of inactivated virus at 8 to 12 weeks followed by an annual booster is generally protective.
- Myxomatosis is a lethal, generalized viral disease of rabbits. It is endemic in wild rabbit populations and in *Sylvilagus* spp. It commonly occurs in the Pacific states of the United States in warmer months. The virus is spread passively on the mouthparts of mosquitoes and fleas. Outbreaks in farmed, laboratory, and pet rabbits result from spillover in wild rabbit populations. A single-dose vaccination of inactivated virus at 8 to 12 weeks followed by an annual booster is generally protective.
- Rabbit fibroma virus is endemic in *Sylvilagus* spp in North America. It is spread by mosquitoes and causes a cutaneous fibroma at the inoculation site with no systemic signs of disease. The fibroma generally regresses within 3 to 4 weeks of infection. It is one of the most common causes of cutaneous neoplasms in pet rabbits.
- Cottontail rabbit papillomavirus, also known as Shope papillomavirus, is a cause of papillomas (warts) on nonhaired or thinly haired skin of rabbits. In 66% to 80% of infected rabbits, papillomas develop into carcinomas 8 to 14 months later. The virus is spread from *Sylvilagus* spp to rabbits by mosquitoes. Infection is uncommon.
- Rabbit oral papillomavirus occurs naturally in rabbits and is widespread among domestic rabbits in Europe and the Americas, particularly young animals. The papillomas are localized mostly on the underside of the tongue and usually regress spontaneously within a few weeks to a few months.
- The multifactorial enteritis complex of juvenile rabbits can be caused by bacteria, viruses, and parasites. Several different viruses have been isolated from rabbits with diarrhea, such as rotavirus, coronavirus, and astrovirus. Whether natural outbreaks of enteritis can be caused by these viral agents alone or in conjunction with other pathogens (eg, *Clostridia* spp, *Escherichia coli,* and coccidia) is not clear.

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INTRODUCTION

Viral diseases in rabbits are infrequently encountered by clinicians seeing pet rabbits in North America. Occasionally myxomatosis may be seen. The situation is different in Europe and Australia where myxomatosis and rabbit hemorrhagic disease, the major viral diseases affecting European rabbit (Oryctolagus cuniculus) populations are endemic. This review considers viruses affecting rabbits by their clinical significance. Viruses of major and minor clinical significance are described, and viruses of laboratory significance are mentioned.

VIRAL INFECTIONS OF MAJOR CLINICAL SIGNIFICANCE

Rabbit Hemorrhagic Disease Virus: Rabbit Hemorrhagic Disease

Introduction

Rabbit hemorrhagic disease (RHD) was first described in China in 1984 in a shipment of Angora rabbits (*Oryctolagus cuniculus*) from East Germany. The disease is characterized by fulminant hepatitis with a case fatality rate of more than 90% in adult rabbits. RHD is caused by a calicivirus termed Rabbit Hemorrhagic Disease Virus (RHDV) (Family: Caliciviridae; Genus: *lagovirus*), which since 1985 has spread to or emerged in Europe in wild and domestic rabbits, and in domestic rabbits in Asia, the Middle East, North Africa, and the Americas. RHDV was deliberately released in Australia and New Zealand as a biologic control for European rabbits and is now established in the wild in these countries (**Table 1**).[1]

The United States has experienced 4 sporadic incursions of RHDV, the first of which occurred in Iowa in 2000.[2] In 2001, an outbreak of RHD was reported in Utah and was traced to a shipment and subsequent outbreak in Illinois.[3] A second isolated outbreak occurred in 2001 in New York and is suspected to have resulted from the importation

Table 1
Viral infections of rabbits

	Disease Caused
• **Viruses of Major Clinical Significance**	
Rabbit hemorrhagic disease virus	Rabbit hemorrhagic disease
Myxoma virus	Myxomatosis
• **Viruses of Minor Clinical Significance**	
Rabbit fibroma virus (Shope fibroma virus)	Rabbit fibromatosis
Lapine rotavirus	Rotaviral infection (Rotaviral diarrhea)
Cottontail rabbit papillomavirus (Shope papillomavirus)	Rabbit papillomatosis
Rabbit oral papillomavirus	Oral papillomatosis
Herpesvirus: Herpes simplex	Herpes encephalitis
Herpesvirus: Leporid-4	Systemic herpesvirus infection
• **Viruses of Laboratory Significance**	
Astrovirus	Enteric disease (?)
Bornavirus	Borna disease
Rabies virus	Rabies
Vaccinia virus	Rabbitpox (Rabbit plague)
Pleural effusion disease virus (infectious cardiomyopathy virus)	Pleural effusion disease and cardiomyopathy
Rabbit enteric coronavirus	Coronaviral enteritis

of rabbit meat from China.[4] The most recent outbreak of RHD was in 2005 and occurred in Indiana.[5] Each outbreak was contained, and was the result of a separate but indeterminable introduction of RHDV rather than from a single virus lineage.[4]

Caliciviruses closely related to RHDV, but generally avirulent or of low virulence, have been identified in domestic and wild rabbits in Europe[6,7] and Australia[8–10] and domestic rabbits in the United States (Michigan rabbit calicivirus)[11] and their presence inferred by serology in rabbit populations on various islands[12,13] and New Zealand.[14] These viruses have been termed rabbit caliciviruses (RCVs) to distinguish them from the lethal RHDV. Viral monitoring indicates that more virulent variants of RCVs, which are genetically distinct from RHDV, are emerging in Europe.[15,16] A related lagovirus, European Brown Hare Syndrome virus (EBHSV), emerged in Europe around the same time as RHDV but does not cause disease in European rabbits. EBHSV may not be as species-specific as RHDV.[1]

Epidemiology

RHDV is specific for European rabbits (*Oryctolagus cuniculus*). Probably all ages are susceptible to infection but young rabbits less than 4 weeks of age rarely develop lethal disease. This age-based protection is lost between 4 and 12 weeks of age.[17] There is no gender predisposition. Young rabbits may be more susceptible to an emergent virulent variant of RCV.[15]

RHDV is infectious by virtually all routes of administration but oronasal infection is probably the most common natural route of infection; conjunctival inoculation by flies may also be important.

Infected rabbits shed RHDV in all secretions. The virus is robust and persists for prolonged periods particularly in rabbit carcasses or on fomites.[18,19] RHDV is spread by direct contact between rabbits or indirectly between susceptible rabbits and carcasses or contaminated environments. It is spread by flies feeding on carcasses, which contain very high concentrations of virus particularly in the liver, and experimentally can be spread mechanically by fleas and mosquitoes.[20,21] Because of the extreme concentrations of virus in carcasses, predator or scavenger species of birds and mammals may also aid spread in the wild, as virus can pass both unchanged and infectious through the gut, and be shed in the feces.

Strong seasonality may be present in wild populations, where most adults have survived infection and are subsequently immune. During the breeding season, as young rabbits gradually lose protection provided by maternal antibody, they provide a susceptible population for RHDV to spread. Epidemics in wild rabbits provide the potential for virus to spread into farmed or domestic rabbits via insects, fomites, or direct contact.

Epidemiology of RHDV, both in wild and farmed rabbits, may be strongly influenced by the circulation of RCV strains, which in some circumstances can provide cross-protection to RHDV.[6,8,22–26]

Clinical presentation

Peracute disease There is sudden death with no premonitory signs; rabbits may be observed grazing normally immediately before death (**Fig. 1**A). Death can occur within 30 to 36 hours of oral infection and as early as 24 hours after injection of virus.

Acute disease Rabbits appear quiet and reluctant to move; they may have an elevated temperature and raised heart and respiratory rates for 24 hours before death. Death usually occurs within 48 to 72 hours after infection.

Subacute disease In subacute disease, there are signs of liver failure, including icterus (see **Fig. 1**C); death occurs over days to several weeks.

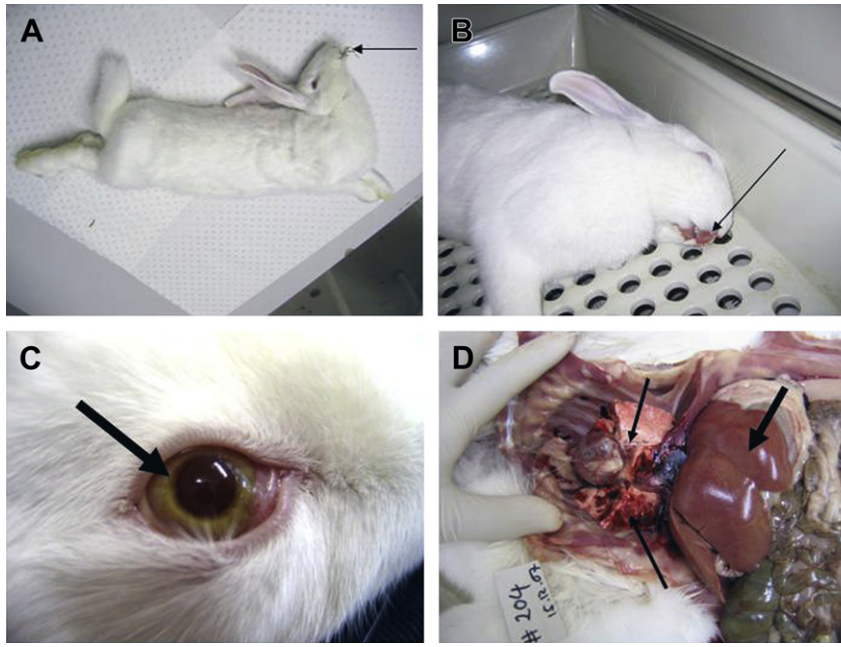

Fig. 1. Rabbits with rabbit hemorrhagic disease. (*A*) Rabbit that died of RHD during a convulsion. Notice how food is still in the mouth (*arrow*). (*B*) Blood from nose and mouth (*arrow*) of a rabbit that died of acute RHD. (*C*) Icteric iris (*arrow*) in albino rabbit with chronic RHD. (*D*) Necropsy of a rabbit that died of RHD. Notice the pale liver (*thick arrow*) and hemorrhages in the lungs (*thin arrows*). (*Courtesy of* Tanja Strive, PhD, CSIRO Entomology, Black Mountain, Australia.)

Subclinical disease A small proportion of infected adult rabbits clears the virus and seroconverts with few or no clinical signs of disease. Young rabbits less than 4 to 5 weeks of age rarely develop disease following infection, although they shed virus, may have a raised temperature, and deaths do occur.

History There is sudden death in adult or subadult rabbits, possibly preceded by 24 hours of quietness/depression with elevated respiratory rate and temperature. Lateral recumbency, coma, and convulsions may be observed before death. Blood from the nose or hematuria may be present (see **Fig. 1**B). In rabbitries, an epidemic with extreme mortality rates in adult and subadult rabbits but not in very young rabbits is typical.

Clinical examination Depression, elevated temperature (up to 42°C), raised respiratory rate, convulsions, ataxia, posterior paresis, and central nervous system depression may occur. Hematuria, bloody diarrhea, and blood from the nares or mouth may be present (see **Fig. 1**B). Pronounced jaundice may be seen in rabbits that have survived more than a few days after infection.

Pathophysiology

RHDV replicates to high titers in the liver, inducing acute hepatic necrosis and fulminant liver failure (see **Fig. 1**D); disseminated intravascular coagulation, hepatic encephalopathy and nephrosis may occur because of the acute hepatic necrosis.[27,28]

Diagnosis

Initial database Leukopenia (lymphopenia and neutropenia) with moderate reduction in thrombocytes but normal erythrocyte numbers[29]; elevated liver enzymes: serum alanine amino transferase (ALT), aspartate amino transferase (AST), lactate dehydrogenase (LDH); alkaline phosphatase (AP) and γ-glutamyltransferase (GGT) are dramatically elevated by 36 to 48 hours after infection; increased serum bilirubin; hypoglycemia; hyperlipidemia; significantly elevated blood urea nitrogen (BUN) and creatinine; increased prothrombin time and decreased factor V and factor VII are all present by 36 to 48 hours after infection.[28–32]

Advanced/confirmatory testing

Necropsy Pale, swollen liver with pronounced lobular pattern and possible focal hemorrhages may be the only major necropsy finding (see **Fig. 1**D). Additional findings include very enlarged, dark spleen; dark-colored kidneys; congested or hemorrhagic lungs with fluid/froth in the trachea (see **Fig. 1**D); hyperemic tracheal mucosa; and ecchymotic and petechial hemorrhages in intestinal and bladder walls and in subcutaneous tissues.

Histopathology Histopathology includes coagulative necrosis of hepatocytes at the periphery of the lobule; thrombi in renal and pulmonary blood vessels (disseminated intravascular coagulation); nephrosis; and lymphocyte depletion from spleen. Subacute cases may show signs of liver regeneration with connective tissue and bile duct proliferation and large, pale-staining binucleate hepatocytes.[27,33]

Virology RHDV cannot be grown in tissue culture. Reverse transcriptase polymerase chain reaction (RT-PCR) is the most common diagnostic tool. Viral RNA can be detected in most tissues, including blood, but the highest concentration is in the liver. Low levels of RHDV RNA can persist for prolonged periods in rabbits that survive infection[34–36] and, depending on the specificity of the assay, nonpathogenic RCV strains may cross-react, so care is needed in interpretation of RT-PCR results in the absence of liver pathology. Hemagglutination of human red blood cells is used as a diagnostic test for RHDV, but not all strains hemagglutinate, and the assay is much less sensitive than RT-PCR; capture enzyme-linked immunosorbent assay (ELISA) using clarified liver homogenates can also be used to demonstrate virus but again is much less sensitive than RT-PCR. Immunostaining of liver sections or impression smears using specific monoclonal antibodies can be used to detect RHDV antigen.[37] Electron microscopy on liver homogenates can demonstrate calicivirus particles in negative stained preparations.[37]

Serology Infected juvenile rabbits or surviving adults develop very high titers of antibody to RHDV capsid protein. Indirect and competition ELISAs are used to demonstrate specific serum antibody to RHDV and isotype ELISAs can be used to demonstrate IgG, IgM and IgA.[37] Hemagglutination inhibition tests can also be used but have largely been replaced by ELISA because of the increased sensitivity and convenience. Serologic cross-reaction with avirulent RCVs occurs, so care is needed when interpreting serologic results.[38] Competition ELISA is more specific than indirect or isotype ELISAs.

Treatment

There is no specific treatment; supportive care only. Experimentally, treatment with melatonin (starting at the time of infection) or cardiotrophin (starting at 12 hours post infection) reduced liver damage, and cardiotrophin also increased survival rates.[39–42] Vaccination in the face of an outbreak is used in rabbitries to bring the

disease under control, as vaccinated animals quickly develop protective immunity. Infected rabbits should be isolated to prevent transmission.

Prognosis and outcome

Prognosis is extremely guarded. Most clinically affected rabbits will die; subacutely infected animals may survive depending on the degree of liver damage and damage to other tissues; chronic liver disease including cirrhosis may result.

Prevention

Vaccination using an adjuvanted, inactivated whole virus vaccine is generally protective. A single dose at 8 to 12 weeks is followed by an annual booster. The vaccine manufacturer's recommendations should be followed. It is not clear if maternal antibody interferes with earlier vaccination but if this is necessary, it may be advisable to give a booster at 10 to 12 weeks of age. Antigenic variants of RHDV/RCV that overcome vaccination have been reported.[15,16,43]

A combined inactivated RHDV vaccine plus a live myxoma virus vaccine in a single-dose formulation is available (Dercunimix, Merial, Lyons, France). A recombinant Myxoma virus vaccine expressing the RHDV capsid protein has recently been released (Nobivac Myxo-RHD, MSD-Animal Health, Hoddesdon, Hertfordshire, UK) as a combined live vaccine to provide protection against myxomatosis and RHDV.[44] A single dose is recommended in rabbits older than 5 weeks of age.

Incoming rabbits should always be quarantined to prevent introduction of disease.

Myxoma Virus: Myxomatosis

Introduction

Myxoma virus (MYXV) (Subfamily: Chordopoxvirinae; Genus: *leporipoxvirus*) causes the lethal, generalized disease myxomatosis in domestic and wild European rabbits (*Oryctolagus cuniculus*). The virus naturally circulated in tapeti *(Sylvilagus brasiliensis)* in South America; however, following deliberate introductions into Australia and Europe as a biologic control for wild European rabbits, MYXV now is endemic in wild European rabbit populations and can spill over into farmed, laboratory, and pet rabbits. MYXV has also been successfully introduced into Chile and Argentina to control feral European rabbits. A closely related virus, often called Californian myxoma virus, is found in *Sylvilagus bachmani* (brush rabbit) in the Pacific states of the United States and the Baja peninsula of Mexico (**Table 2**). This virus is also highly lethal in European rabbits.[45]

Table 2
Lagomorph viruses: transmission between *Oryctolagus* and *Sylvilagus* and severity of induced disease

Virus	*Oryctolagus* European Rabbit		*Sylvilagus* American Cottontail
• **Poxviridae**			
Myxoma virus	Myxoma	←	Fibroma[a]
Rabbit (Shope) fibroma virus	Fibroma, mild	←	Fibroma, severe[a]
• **Papillomaviridae**			
Cottontail rabbit (Shope) papilloma virus	Papilloma, SQC 75%	←	Papilloma, SQC 25%[a]
Oral papilloma virus	Oral papilloma[a]	→	Oral papilloma

Abbreviation: SQC, squamous cell carcinoma.
[a] Natural host.

Epidemiology

Myxomatosis is essentially a disease of European rabbits, although European hares may rarely develop generalized disease.[46] There is no age or sex predilection but very young rabbits may die without obvious myxomatosis. Passively transmitted maternal antibody may modify the disease outcome in young rabbits born to immune does.[47]

The virus is spread passively on the mouthparts of biting arthropods, predominantly mosquitoes and fleas (but also Culicoides midges and lice), that probe through the virus-rich cutaneous lesions when seeking a blood meal. The virus does not replicate in the vector.[48]

Contact spread from rabbit to rabbit may also occur from virus shed in ocular and nasal secretions or from the surface of eroded skin lesions[46]; virus is also potentially present in semen and genital secretions. Oral infection is very inefficient so conjunctival or nasal inoculation is probably necessary for transmission. Aerosol transmission is inefficient but virus is readily transmitted on fomites, such as water bottles or feeders, or by handlers.

In Europe and Australia, wild European rabbits act as reservoirs for MYXV and mosquitoes can transmit the virus to domestic rabbits. Where there is close proximity between wild and domestic rabbits, fleas and direct contact may also transmit virus.

In South America, vector transmission from *S brasiliensis* to farmed, laboratory, or pet rabbits occurs.[46] Similar spillover occurs from *S bachmani* in the Pacific states of the United States and Mexico.[49–53]

Seasonality is driven by the availability of vectors and the epidemiology of the disease in wild rabbits. In rabbitries, introduction of rabbits carrying the disease (including vaccinated rabbits) has led to epidemics.[54] Introduced semen may also pose a risk.[55]

Clinical presentation

Disease forms

Peracute myxomatosis Peracute myxomatosis may present as sudden deaths with only mild or no clinical signs of myxomatosis, particularly with Californian MYXV infections. Neurologic signs, such as convulsions, have been described.[46] In Australia, some field strains cause acute pulmonary edema in domestic rabbits. Death typically occurs 7 to 15 days after infection.

Acute myxomatosis Acute myxomatosis is the classic mucocutaneous form of myxomatosis with multiple skin lesions (**Fig. 2**A); a second amyxomatous form with fewer skin lesions has been described in Europe.[55–58] Australian field isolates may also present as essentially amyxomatous in domestic rabbits. Case fatality rates are nearly 100%, but in some individuals, the disease course may be prolonged. Death typically occurs 10 to 15 days after infection.

Subacute myxomatosis Natural selection in European rabbits in Australia and Europe has seen the emergence of attenuated field strains of MYXV.[59,60] These viruses cause typical myxomatosis but with a protracted course (see **Fig. 2**B); case fatality rates may be less than 50% to more than 95%, with deaths occurring from 10 to 30 plus days after infection. Survivors may be left with chronic respiratory disease.

History and physical examination Very early cases present with slight eyelid swelling, conjunctivitis, and thickened ears (see **Fig. 2**A); temperatures may be elevated above 40°C but this is variable. Depending on the virulence of the virus, this may be 5 to

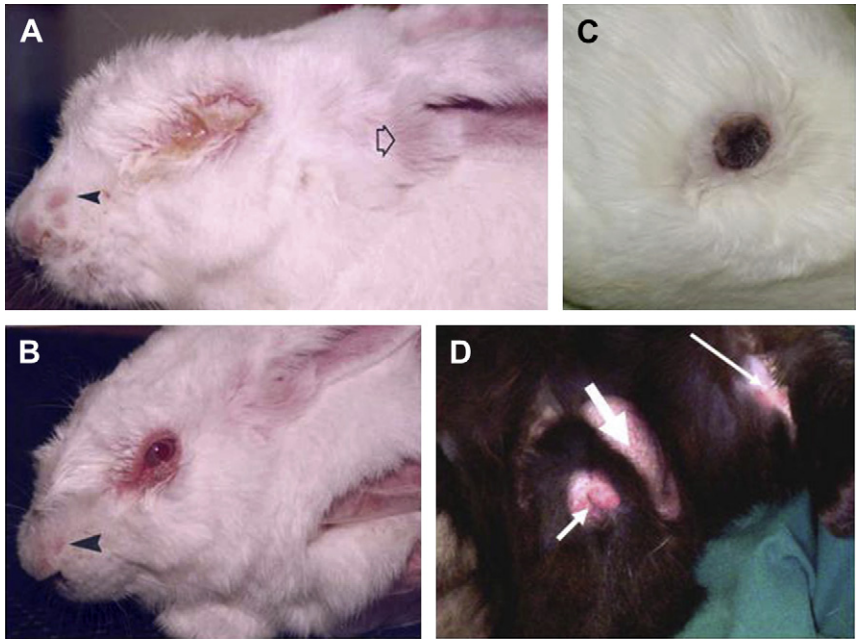

Fig. 2. Clinical appearance of rabbits with myxomatosis. (*A*) Acute myxomatosis caused by virulent myxoma virus. Skin lesions are present on the nose (*solid arrowhead*). The base of the ear is swollen (*open arrowhead*) and the eyes are closed with mucopurulent conjunctivitis. (*B*) Rabbit infected with attenuated strain of myxoma virus. The eyelid margins are red and swollen and serous discharge is present. Swelling is noted around the face and nose (*arrowhead*). (*C*) Scabbed skin lesion (approximately 2.5-cm diameter) at primary infection site. (*D*) Swollen testis (*broad arrow*); swollen genital opening (*short arrow*); secondary skin lesions (*narrow arrow*). ([*A, B*] *From* Best SM, Kerr PJ. Coevolution of host and virus: the pathogenesis of virulent and attenuated strains of myxoma virus in resistant and susceptible European rabbits. Virology 2000;267(1):36–48; with permission.)

10 days after infection. Careful examination may reveal a 1-cm to 2-cm diameter, raised, reddened primary cutaneous lesion, but the size and thickness of this varies enormously with the strain of virus (see **Fig. 2**C).

Later in the disease course, rabbits present with swollen eyelids and mucopurulent blepharoconjunctivitis in which the eyes may be partially or completely closed by the eyelid swelling (there is no involvement of the eye itself). The face is swollen and the ears swollen and drooping or just thickened, particularly around the base (see **Fig. 2**A).

Mucopurulent nasal discharge is common and the nasal passages may be occluded causing a gasping, stertorous respiration with extension of the head and neck.

Severe swelling of the anogenital region is typical and in males, orchitis and epididymitis together with gross swelling of the scrotum occur (see **Fig. 2**D).[61]

In the classic mucocutaneous form of myxomatosis, cutaneous lesions ranging from a few millimeters to 5 to 6 cm in diameter and from 1 to 20 mm high occur over the eyelids, face, ears, and scrotum and late in the disease can be palpated over the body, legs, and feet. In late infections, or in recovering rabbits, the surface of the cutaneous lesions may be hemorrhagic, black, or scabbing (see **Fig. 2**C).

Popliteal and prescapular lymph nodes are grossly enlarged and readily palpable.

Temperatures may be as high as 41°C but often drop below normal before death.

Rabbits may continue to eat and drink until quite late in the disease course but severe weight loss is common and dehydration may occur.

Pathophysiology

Virus inoculated into the dermis/epidermis by biting arthropods replicates locally in macrophages/dendritic cells and then in epidermal cells.[62] Proliferation of the epidermal cells and mucoid swelling of the underlying dermis forms the raised primary lesion that is sometimes referred to as a myxoma or tumor. From the primary site, MYXV is transported to the draining lymph node where it replicates in T cells, macrophages, and other cells, causing almost complete loss of T cells. From the draining lymph node, it disseminates in lymphocytes and possibly macrophage/monocytes to distal tissues, such as lungs, spleen, testes, skin, and mucocutaneous sites, such as eyelids. Virus replication at distal skin sites causes the secondary cutaneous lesions found over the body.[62–64]

The cause of death in acute classic myxomatosis is obscure; major organs are typically not severely damaged.[65] MYXV profoundly suppresses innate and adaptive immune responses, although low titers of IgM and IgG and even neutralizing antibody can be detected before death.[45,64,66–70] Secondary bacterial infections of the conjunctivae, upper respiratory tract, and lungs are typical in rabbits that survive longer than 10 to 14 days after infection and may be the major cause of death in rabbits infected with subacute strains of MYXV. Rabbits free of *Pasteurella multocida* and *Bordetella bronchiseptica* appear to have fewer complications before death, but even these may have lobar pneumonia at necropsy.

Diagnosis

Clinical signs of classic myxomatosis are fairly clear-cut, although bacterial upper respiratory tract infections can cause confusion and misdiagnosis.[55] Hematology is generally unremarkable: neutrophilia, lymphopenia, and lymphocytosis can all be seen at different stages depending on the virulence of the virus.

Necropsy findings are largely limited to the external lesions and features already described, and depend on the time of death and the underlying virulence of the virus. The cutaneous lesions are clearly separated from the underlying tissue and have a glistening, mucoid appearance on the cut surface. Lymph nodes are grossly enlarged, sometimes hemorrhagic, and may have a watery consistency on section. The spleen is generally 2 to 3 times normal size and often dark-colored. In males, scrotal edema of 0.5 to 1.0 cm may be obvious on incising the skin. In peracute cases, pulmonary edema may be the cause of death with the trachea and bronchi full of froth and fluid, and the lungs dripping fluid. Hemorrhages on serosal membranes and intestinal and stomach walls may be present in some cases.

Confirmatory testing Histopathology of cutaneous lesions is characterized by cellular proliferation and cell death.[71] In the epidermis, the epidermal cells proliferate, enlarge, and undergo ballooning degeneration; the underlying dermis is edematous with complete disruption of the connective tissue architecture; the endothelium of the small blood vessels is disrupted by large stellate or polygonal “myxoma cells.” These cells appear to migrate from the blood vessels into the dermis where they are often surrounded by polymorphs. In infections with virulent virus, there may be an influx of polymorphs into the dermis, particularly at the base but lymphocytes are rarely present.[62] In lymphoid tissues, complete loss of lymphocytes from both B-cell and T-cell zones can occur together with proliferation of reticular cells that obliterate the sinuses; disruption of the small blood vessels by myxoma cells is similar to that in the epidermis and polymorphs may be prominent. The presence of virus can be confirmed by

immunostaining of epidermal sections from the nodular lesions or eyelids. Negative-stained electron microscopy can be used to identify virus eluted from skin sections.[72]

PCR, using specific oligonucleotide primers for MYXV, can be done on DNA extracted from biopsies, conjunctival swabs, or tissues collected at necropsy. Virus titers in blood are generally low but the white cell fraction could be used for PCR in early/acute cases. A 1-mm dermal punch biopsy from a lesion yields sufficient DNA for diagnostic PCR.

MYXV can be readily cultured from cutaneous lesions or eyelids (biopsied or collected at necropsy) or from conjunctival swabs. The virus grows in various rabbit cell lines, including RK-13 and SIRC, and other mammalian cell lines, such as Vero and BGMK, and on the chorioallantoic membrane of embryonated chicken eggs. Tissues and swabs in 1:1 glycerol/saline or glycerol/phosphate-buffered saline can be stored at –20°C for some weeks before processing but for prolonged storage should be kept at –80°C.

Specific antibody can be detected as early as 6 to 10 days after infection using ELISA and persists for at least 12 months. Other serologic assays include complement fixation, virus neutralization, and gel immunodiffusion; these are less sensitive than ELISA.[72] Gel immunodiffusion can also be used to detect viral antigen.

Differential diagnosis

- Bacterial respiratory tract infections (eg, pasteurellosis)
- Bacterial conjunctivitis/keratoconjunctivitis
- Rabbit systemic herpesvirus infection, a recently described virus (leporid 4 herpesvirus) in North America causing swollen head, mucopurulent conjunctivitis, nodular hemorrhagic skin lesions, and respiratory distress.[73]

Treatment

At present, no specific treatment exists for myxomatosis. If the decision is made to attempt treatment, careful monitoring is necessary to avoid prolonging suffering. The aims of treatment should be to provide nursing support, control secondary infections, and minimize distress. Cessation of food and water intake, ongoing severe weight loss, or rectal temperature below 38°C is grounds for euthanasia.

Infected rabbits should be kept warm. There is evidence that high temperatures ameliorate the effects of attenuated viruses[74]; food intake and hydration should be carefully monitored. Broad-spectrum antibiotics, such as fluoroquinolones, potentiated sulfonamides, or tetracyclines, could be used but there is no clear evidence supporting their use and antibiotic treatment had no impact on the disease caused by virulent virus.[75] For analgesia, buprenorphine 0.03 mg/kg twice daily has been used in acute myxomatosis but appeared to have little impact on rabbit behavior compared with untreated rabbits.[76]

An orally active derivative of cidofovir, CMX001, has activity against MYXV in vitro (G. McFadden, personal communication, 2009) and against the orthopoxvirus rabbitpox in rabbits in vivo but is available only experimentally.[45,77,78]

Prognosis and outcome

Highly virulent strains of MYXV have essentially 100% case fatality rates in domestic rabbits. Attenuated strains of MYXV may have case fatality rates of less than 50% to more than 95%, but the clinical course of the disease is prolonged. Rabbits infected with attenuated strains may recover over 2 to 3 weeks; in these rabbits, the cutaneous lesions become circumscribed and clearly demarcated from the surrounding skin, scab, and dry out, often leaving a scarred “moth-eaten” appearance of the face and ears. Chronic respiratory disease, such as snuffles, is common in surviving rabbits;

some surviving rabbits do not gain weight and may have more serious underlying secondary infections, such as bacterial pneumonia. Even in apparently recovered rabbits, it is not unusual to find complete consolidation of cranial lung lobes at necropsy.

Prevention

Vaccination Immunization with live attenuated strains of MYXV (e.g. Dervaximyo SG33, Merial, Lyons, France) or the heterologous rabbit fibroma virus (RFV) (Nobivac Myxo, MSD-Animal Health, Hoddesdon, Hertfordshire, UK) is used to protect rabbits against myxomatosis in Europe.[79] The homologous live vaccines appear to provide longer lasting protection than vaccination with RFV but some have been associated with immunosuppression in young rabbits. This has led to recommendations to vaccinate initially with RFV followed by a boost with attenuated MYXV.[80,81] The Australian federal government does not permit commercial use of myxomatosis vaccines in domestic rabbits in Australia.

Neither type of vaccine provides 100% protection against high-dose challenge and protection can be quite short-lived (3–12 months). Vaccinated rabbits can become infected on challenge and shed virus.

Other preventive measures

- Prevention of contact with wild rabbits and screening of cages/buildings to prevent mosquito transmission. Elimination of other vectors, such as rabbit fleas, lice, and mites.
- Quarantine of incoming rabbits to prevent introduction of rabbits incubating the disease. Even vaccinated rabbits should be quarantined.
- Isolation of suspected clinical cases and in-contact rabbits until diagnosis is confirmed.

VIRAL INFECTIONS OF MINOR CLINICAL SIGNIFICANCE

Rabbit Fibroma Virus (Shope Fibroma Virus): Rabbit Fibromatosis

Introduction

Rabbit fibroma virus (RFV) (Subfamily: Chordopoxvirinae; Genus: *leporipoxvirus*) circulates in Eastern cottontail rabbits (*Sylvilagus floridanus*) in North America (see **Table 2**). It is genetically and antigenically closely related to myxoma virus, but in European rabbits (*Oryctolagus cuniculus*) RFV normally causes only a cutaneous fibroma at the inoculation site with no systemic signs of disease. In suckling rabbits, more generalized disease and death usually occur.[82,83] RFV is used as a live virus heterologous vaccine against myxomatosis.[79,84]

Epidemiology

RFV causes cutaneous fibromas in *S floridanus* usually on the feet (**Fig. 3**A), legs, or muzzle[85]; virus is spread passively on the mouthparts of biting arthropods (predominantly mosquitoes) that probe through the fibroma seeking a blood meal; fleas can transmit the virus but experimentally seemed relatively inefficient.[86,87] European rabbits may be infected by mosquitoes (or possibly by fleas if in close contact with Eastern cottontail rabbits) from this natural reservoir of the virus. The highest risk is during the autumn when large populations of infected cottontail rabbits and mosquitoes may coexist. The virus is reported in the Eastern and Midwest states of the United States, including Texas, and in Ontario, Canada.[46,88] Experimentally, mosquito transmission from immunocompetent European rabbits is inefficient, despite high titers of virus in the fibroma, so the European rabbit is essentially a dead-end host and virus

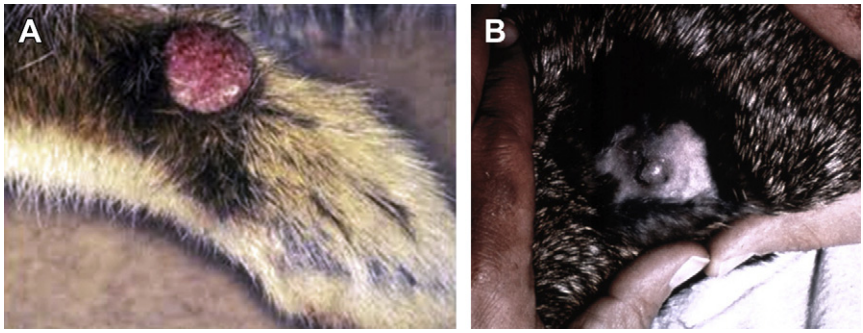

Fig. 3. (*A*) Nodular fibromatous growth on forepaw of Eastern cottontail rabbit naturally infected with rabbit (Shope) fibroma virus. (*B*) Experimentally induced Shope fibroma on the dorsum of a pigmented rabbit 21 days post inoculation. The fibroma is freely movable in the subcutaneous tissue. ([*A*] *Image from* Department of Veterinary Pathology, Armed Forces Institute of Pathology, Washington, DC.)

spread from either naturally infected or vaccinated rabbits would be unlikely.[48,89,90] However, suckling rabbits or immunosuppressed adult rabbits in which the immune response fails to clear the fibroma can act as sources for mosquito transmission.[90,91] Direct rabbit-to-rabbit spread does not occur,[82] but mechanical spread between rabbits is theoretically possible. Virus dropped into the conjunctivae or nose will infect rabbits. Natural outbreaks in commercial rabbitries have been reported in the United States.[88,92] In a 16-year retrospective study of cutaneous neoplasms in pet rabbits from the University of Pennsylvania veterinary school, 10.5% of skin tumors were RFV-induced fibromas.[93]

Clinical presentation

Skin nodules 0.5 to 6.0 cm in diameter are typically found on the forepaws, ears, and head. There may be multiple discrete nodules, freely moveable with no underlying tissue connections (see **Fig. 3**B). Usually no systemic signs of illness occur except in suckling rabbits where more generalized disease and death may ensue.[82,83,88] The fibromas generally resolve within 3 to 4 weeks of infection.[84]

Pathophysiology

There is a solid tumorlike nodule, glistening and mucoid on cut surface; it may be necrotic in the center with scabbing of overlying epidermis. Histologically, it is described as a fibroxanthosarcomalike tumor.[94,95]

Diagnosis

Diagnosis is made from clinical appearance and history; histopathology; virus isolation (RFV is readily cultured in rabbit cell lines, such as RK-13 or SIRC, and on the chorioallantoic membrane of embryonated chicken eggs); demonstration of poxvirus particles using thin-section electron microscopy on fibroma sections; or amplification of RFV DNA using PCR on DNA extracted from fibroma tissue collected at necropsy or biopsy.

Treatment

No treatment is normally necessary.

Prognosis and outcome

In all but suckling rabbits or experimentally immunosuppressed rabbits, the disease is not normally significant.

Prevention

Shield lactating does and their litters from mosquitoes.

Lapine Rotavirus: Rotaviral Enteritis

Introduction

Rotaviruses (Family: Reoviridae) are a major cause of diarrhea in intensively reared animals throughout the world. Essentially, every species of domestic animal and bird harbors at least one indigenous rotavirus that typically is responsible for causing diarrhea in newborn animals. The clinical signs, diagnosis, and epidemiology of disease are similar in all species; the severity of disease ranges from subclinical, through enteritis of varying severity, to death.

The classification of rotaviruses is based on genotypic and serologic analyses. Variation in the group-specific capsid antigen on VP6 defines the 6 major groups A to F. Rabbit rotaviruses are typically group A rotaviruses.[96–98] Differentiation into serotypes is based on neutralization tests. Because both outer capsid proteins (VP4 and VP7) carry type-specific epitopes recognized by neutralizing antibodies, a binary system of classification of serotypes has developed, similar to that used for influenza viruses. For example, in group A rotaviruses, 14 G serotypes have been defined on the basis of differences in VP7, and 14 P serotypes based on differences in VP4.[99]

Epidemiology

Rotavirus is an important and common disease agent in commercial rabbitries. It is rarely diagnosed in pet rabbits. Serologic surveys of commercial rabbitries in Europe[100–104] and North America,[105,106] laboratory research rabbits,[107] Eastern cottontail rabbits (*S floridanus*),[108] and hares (*Lepus* spp)[108,109] indicate lapine rotaviruses are widespread. In many commercial rabbitries, rotavirus infection is likely enzootic, as rotaviruses can survive in feces for several months.

Rotaviruses are excreted in the feces of infected animals in high titer (up to 10^{11} viral particles per gram); shedding of virus can occur for 6 to 8 days from the second to fifth day postinfection.[110] Some rotaviruses are highly resistant to chlorination, and can survive for long periods in water, so that water-borne transmission is also a risk.[111]

Most viruses with multisegmented double-stranded RNA genomes, such as rotavirus, are included in the family Reoviridae. Because of their segmented RNA genomes, reassortment of genome segments among different strains of rotavirus is common, as is a high rate of RNA mutations in individual genes.[112] The resulting genetic shift and drift leads to a remarkable diversity of rotaviruses, reflected by the numerous serotypes and strains of virus. Consequently, infection with new strains of rotavirus is common in breeding facilities.

Clinical presentation

Rotavirus infection in rabbits younger than 2 weeks old is characterized by voluminous, soft to liquid feces.[113] Some affected animals are only moderately depressed, and often continue to suckle or drink milk.[106,110] Rabbits older than 2 weeks of age typically do not show diarrhea because of the fluid absorptive capability of the cecum.[113] Other factors, particularly reduced colostrum intake, but also infections with other enteric pathogens, such as *Escherichia coli*, poor hygiene, chilling, and overcrowding, contribute to the severity of disease.[104,105] Young animals may die because of dehydration or secondary bacterial infection.

During epizootic infections, suckling rabbits may experience high mortality. During enzootic infections, suckling rabbits receive maternal antibody transplacentally, and experience low mortality but high morbidity.[114]

Pathophysiology

Rotavirus infections cause intestinal malabsorption and maldigestion by destruction of the terminally differentiated enterocytes lining the tips of the intestinal villi. Rotaviruses replicate in mature enterocytes lining intestinal villi, especially in the jejunum and ileum. Damaged villi become shortened and covered with undifferentiated epithelial cells that migrate from the crypts. These cells secrete reduced levels of disaccharidases (eg, lactase); lactose and other disaccharides accumulate in the lumen causing an osmotic drain and attracting fluid into the lumen.[113,115,116] The neonatal bowel is especially susceptible to infection, because of the slow epithelial turnover rate and the high proportion of terminally differentiated epithelium, and is less able to carry out glucose-coupled sodium transport[116] and chloride secretion.[115]

Undigested lactose in the milk promotes bacterial growth and exerts a further osmotic effect; both mechanisms contribute to the diarrhea. In young rabbits, bacterial superinfection with *E coli* and other bacteria (eg, *Clostridia* spp) and coccidia have an additive effect and contribute to the multifactorial enteritis complex of juvenile rabbits.[103,105,117] Mortality can often be high in commercial rabbitries.

Diagnosis

Diagnosis is based on history, age, and characteristic gross and microscopic features. Electron microscopy still allows rapid diagnosis, as virus particles are plentiful in the feces of affected animals, and have a highly distinctive wheel-like appearance (from the Latin *rota* = wheel). ELISA is a more practicable and more sensitive method for detection of rotaviruses in feces in most laboratories. A commercial human rotavirus antigen detection kit has been shown to be effective in laboratory rabbits because of its ability to detect rotavirus antigen in feces.[118] The specificity of enzyme immunoassays can be manipulated by selecting either group-specific or serotype-specific or broadly cross-reactive antibodies as capture and/or indicator antibodies in an antigen-capture assay. Rotaviruses are difficult to isolate in cell culture.[119]

Diagnostic tests that identify the viral genome in RNA extracted directly from feces include polyacrylamide gel electrophoresis, which can distinguish rotavirus groups A, B, and C by RNA electropherotype pattern alone.[112] RT-PCR assay allows the use of primer pairs appropriate for the degree of specificity desired (rotavirus groups based on VP6, or G and P genotypes based on VP7 and VP4).[112] These tests are generally used to make necessary distinctions in molecular epidemiologic studies to identify reassortant viruses and potential interspecies transmission. The rate of success of any diagnostic test for rotavirus is significantly affected by the time of sample collection; samples collected beyond 48 hours after onset of diarrhea are of limited value.[101]

Treatment

Supportive care, including warmth, is critical. Recovery in severely dehydrated rabbits can be aided by administering oral electrolyte solutions containing glucose shortly after the onset of diarrhea.[104] In severe cases that are likely to be "enteritis complex," the value of antibiotics is questionable.

Prognosis and outcome

Prognosis is affected by superinfection with other intestinal pathogens.[103,113,117] Rotavirus antigen has been detected from healthy rabbits (specimens taken one day after weaning and 1 week later) in about 15% of commercial Italian rabbitries.[103]

Prevention

Although the management of intensive rearing units for farmed rabbits can be improved to reduce the incidence of disease, there is little likelihood that improved

hygiene alone can completely control rotavirus infections. Local immunity in the small intestine is more important than systemic immunity in providing resistance to infection; rotavirus antibodies present in immune colostrum and milk are critical in protecting neonates.[114,120] Although much of the colostral antibody enters the circulation, serum antibody levels are not as critical for protection. Inoculation of the dam with inactivated or attenuated rotavirus vaccines promotes higher levels of antibody in the colostrum and milk, and a longer period of antibody secretion in milk, with a corresponding decrease in the incidence of disease in neonates.[121]

Cottontail Rabbit Papillomavirus (Shope Papillomavirus): Rabbit Papillomatosis

Introduction

Cottontail rabbit papillomavirus (CRPV), also commonly known as Shope papillomavirus (Family: Papillomaviridae) is a cause of papillomas (warts) in rabbits. Classic studies on viral oncogenesis were performed in the 1930s[122–124] with CRPV.

Epidemiology

The natural host is the cottontail rabbit (*Sylvilagus* spp) (see **Table 2**).[125] CRPV causes natural disease uncommonly in domestic rabbits.[126,127] Insect vectors (eg, mosquitoes) are probably the cause of mechanical spread of virus from cottontail rabbits to domestic rabbits.

Clinical presentation

CRPV papillomas occur most frequently on nonhaired or thinly haired skin, such as eyelids and ears. In CRPV papillomas, the normal process of keratinization is altered, as evidenced by the hyperkeratosis, parakeratosis, and fragmentation of the horny layer. Consequently, lesions range from a pedunculated, cornified surface overlying a fleshy central area (early papilloma) to multiple conical/cylindrical hornlike masses of firm keratin 3 to 5 mm in diameter and 0.5 to 2.0 cm in length (cutaneous horns) (**Fig. 4**).

Pathophysiology

Warts induced by CRPV in both cottontail rabbits[125] and European rabbits often progress to carcinomas. Virus replication occurs only in the cottontail rabbit,[128] and not the European rabbit, although one strain of CRPV has been shown to replicate at low levels in European rabbits.[129] In domestic rabbits, the tissue surrounding an inoculation site (either experimentally or naturally by mosquitoes) is clinically and histologically normal, but contains viral DNA at low levels detectable by PCR. The latent virus is able to form warts from mild skin irritation.[130] Ultraviolet irradiation will also induce warts, which is why the lesions are typically found on the ears, lips and eyelids: areas without much fur that are exposed to sunlight.[131] Different mRNA transcripts are present (E1 protein, E2 protein, E6 protein, E7 protein, L1 protein, and L2 protein transcripts) in latent viruses. Only E6 and E7 oncoprotein transcripts can be induced to form papillomas.[132] The papillomas develop into carcinomas 8 to 14 months later in 25% of cottontail rabbits and in 66% to 80% of European rabbits.

Diagnosis

The histologic diagnosis is consistent with a squamous papilloma. In contrast to papillomas induced by CRPV, spontaneous nonviral squamous papillomas develop in haired skin. Other causes of skin lesions in rabbits that should be considered in the differential diagnosis include rabbit oral papillomavirus induced conjunctival papilloma and rabbit (Shope) fibroma virus infection. Shope fibromas are typically flattened to

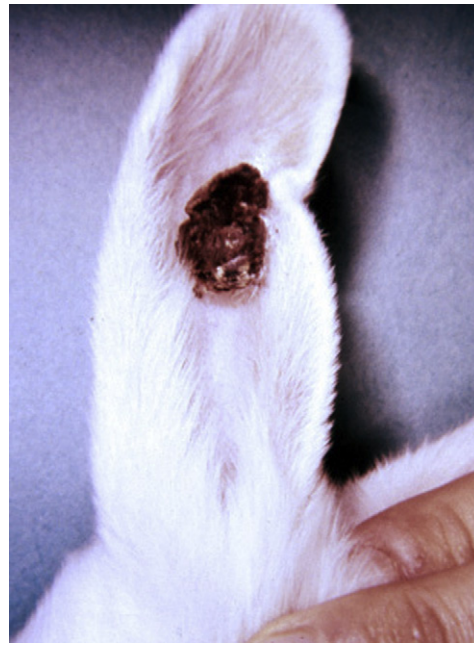

Fig. 4. CRPV-induced papilloma on the ear of a New Zealand white rabbit. Notice how the papilloma shows multiple hornlike masses of firm, protruding keratin.

nodular tumors 0.5 to 6.0 cm in diameter that tend to occur on the forepaws, ears, and head.

Treatment

Intralesional 1% (wt/vol) (0.036 M) cidofovir treatment of rabbit papillomas led to elimination, or "cure" of large papillomas over a 6-week to 8-week treatment period.[133] However, recurrences at periods from 1 to 8 weeks after treatment cessation were observed in approximately 50% of cured sites. Tumor reappearance occurred because of latent virus around the inoculation sites.

Immune stimulation with unmethylated dinucleotides of cytosine and guanine (CpG) have shown efficacy against papillomas as monotherapy, as vaccine adjuvants, and in combination with chemotherapies.[134] Despite the potency of CpG in triggering host immunity, CpG oligodeoxynucleotide has experimentally not shown a therapeutic effect against experimentally induced CRPV papilloma in rabbits.

Surgical excision of papillomas can be attempted, but a wide margin is required. PCR of the edges of excised skin can be used to detect CRPV DNA and determine if all latent infected cells were removed. However, even if one lesion is completely removed, there are likely to be other latent infected inoculation sites in surrounding skin that have the potential to develop into papillomas and eventually carcinomas if E6 and/or E7 oncoproteins are present. If a papilloma occurs on the ear, amputation of the ear is a potential but drastic treatment.

Prognosis and outcome

CRPV papillomas develop into carcinomas 8 to 14 months later in 66% to 80% of infected rabbits. Papillomas undergo immune-mediated regression if they do not

progress to carcinomas. Infection is uncommon. Only 2 CRPV papillomas (1.1%) were identified in a 16-year retrospective study of cutaneous neoplasms in pet rabbits from the University of Pennsylvania veterinary school.[93]

Prevention

Keep rabbits indoors or in insect-protected enclosures to avoid transmission of virus from cottontail rabbits. This is an issue only in North America where cottontail rabbits occur naturally.

If a papilloma is identified, and PCR identifies CRPV, advise owners to keep their rabbit out of direct sunlight and not to irritate (eg, removing incrustations) the papilloma or surrounding skin, as it will induce the occurrence of new papillomas.

Rabbit Oral Papillomavirus: Oral Papillomatosis

Introduction

Rabbit oral papillomavirus (Family: Papillomaviridae) (ROPV) occurs naturally in domestic rabbits (see **Table 2**). The causative papillomavirus is distinct from the cottontail rabbit papillomavirus (Shope papillomavirus).

Epidemiology

ROPV is widespread among domestic rabbits in Europe and the Americas, particularly young animals.[135–138] Lesions typically occur in rabbits between 2 and 18 months of age. The oral papillomas are not highly contagious. Lesions are found more frequently in young rabbits whose mothers have papillomas; transmission from the mother to offspring during suckling is common.[139] ROPV can be recovered from the mouth washings of rabbits having no oral papillomas, as it is latent in the mouth, and does not proliferate unless the mucous membrane is injured.

Clinical presentation

Tumors are small, gray-white, filiform or pedunculated nodules (5 mm in diameter and 4 mm in height) and are localized mostly on the underside of the tongue (**Fig. 5**)[140]; however, one report describes a conjunctival papilloma.[141] The papillomas usually

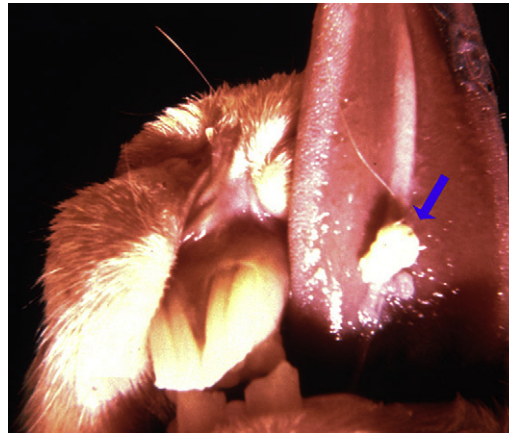

Fig. 5. Rabbit oral papillomavirus tumor presenting as a white pedunculated nodule on the underside of a New Zealand white rabbit tongue (*arrow*). (*Image from* Department of Veterinary Pathology, Armed Forces Institute of Pathology, Washington, DC.)

regress spontaneously within a few weeks to a few months. Most pet rabbit owners do not notice the lesions.

Pathophysiology

ROPV causes papillomas in the oral mucosa of several species of rabbits and hares but fails to cause lesions when inoculated into other rabbit tissues and into the oral mucosa of other species. ROPV differs from the cottontail rabbit papilloma virus (Shope papillomavirus) and homologies between the open reading frames of the 2 viruses vary between 23% and 68%.[142] Rabbits immune to the oral papillomavirus are fully susceptible to cottontail rabbit papilloma virus and vice versa.[142] There is little sequence homology between the genomes of papillomaviruses from different species.[143]

Diagnosis

Lesions are typical squamous papillomas on fibrovascular stalks. Basophilic intranuclear inclusions may be present in the stratum spinosum.[136] Virus particles from lesions may be seen under electron microscopy. Differential diagnosis of oral lesions includes sialoceles.[144]

Treatment and prognosis

Oral papillomas are typically not treated, as they regress spontaneously and show no tendency to malignancy.

Herpes Simplex Virus: Herpes Encephalitis

Introduction

Although rabbits have served as an animal model for herpesvirus encephalitis and keratitis following experimental inoculation with human herpes simplex virus (HSV) (Subfamily: Alphaherpesvirinae; Genus: *simplexvirus*) 4 reports exist of naturally occurring fatal encephalitis in rabbits due to HSV infection.[145–148]

Epidemiology

Owners of rabbits with clinical facial herpesvirus infection are suspected to be the origin of infection. A similar situation has been reported in 2 pet chinchillas (*Chinchilla lanigera*) diagnosed with fatal HSV encephalitis.[149,150]

Viral isolates derived from 2 marmosets and 1 domestic rabbit that died from HSV encephalitis revealed different genotypes, suggesting that certain HSV genotypes with a higher potential of being transmitted to animals do not exist.[147] The infrequency of natural cross-infection between humans and other species has led some researchers to postulate a nonimmunologic protective mechanism against HSV infection in animals.[151]

Clinical presentation

Affected rabbits present with severe signs of central nervous system dysfunction, such as incoordination, intermittent myoclonic seizures, and opisthotonus. In one case, results of hematologic and serum biochemical analyses revealed only lymphopenia, a relative monocytosis, and an increase in serum activity of creatine phosphokinase and serum concentration of total protein.[146]

Diagnosis

All cases described have been diagnosed at necropsy. Histologic evaluation of brain tissue reveals lesions characteristic of severe, diffuse, nonsuppurative meningoencephalitis and a few large, eosinophilic, intranuclear inclusion bodies in neurons and

glial cells. In situ hybridization and/or PCR detect HSV DNA in the nuclei of glial cells, lymphocytes, and neurons.[152]

Treatment

In one case, despite intravenous administration of crystalloid fluids and treatment with antimicrobials, vitamin B complex, nutritional support, and prednisolone, the condition of the rabbit deteriorated and it was euthanized 7 days after admission.[146]

Prognosis and outcome

All cases in rabbits and chinchillas have resulted in death.

Prevention

Owners with active HSV facial lesions should avoid close contact, such as kissing their pet rabbits.

Leporid-4 Herpes Virus: Systemic Herpes Virus Infection

Introduction

A herpes virus designated as leporid herpesvirus 4 (LHV-4) (Subfamily: Alphaherpesvirinae; Genus: *simplexvirus*) that is highly pathogenic for domestic rabbits has been recently described in rabbits in Alaska and Canada.[73,153–155] Analysis of virus samples indicates that the virus is most closely related to bovine herpesvirus-2. The next most closely related viruses are human HSV 1 and 2, and a number of cercopithecine herpesviruses.[156]

Three naturally occurring herpesviruses of rabbits and hares, called leporid herpesviruses 1, 2, and 3 (LHV-1, LHV-2, and LHV-3), have been identified.[156] They have been classified tentatively as belonging to the subfamily Gammaherpesvirus.[156] The best characterized is LHV-3 (*Herpesvirus sylvilagus*), which is endemic in Eastern cottontail rabbits (*S floridanus*) and causes tumorlike lesions in lymph nodes, kidney, spleen, and liver[157]; however, it does not cause disease in domestic rabbits.[156] LHV-2 (*Herpesvirus cuniculi*) causes asymptomatic infections of domestic rabbits.[156] LHV-1 is found in cottontail rabbits[158,159] and no disease has been reported to be associated with it in domestic rabbits.[156] The novel herpes virus identified in Alaska and Canada is referred to as LHV-4.[153]

Epidemiology

Reports to date of LHV-4 infection are limited to commercial rabbitries. Experimental exposure of domestic rabbits to virus isolates results in severe clinical disease and necrosis in the spleen and lymph nodes.[156] Viral DNA has been identified in a variety of tissues by PCR, consistent with a systemic infection.

It is possible that LHV-4 is present in an animal reservoir found in northwestern North America, in which it causes asymptomatic infections and infrequently comes in contact with domestic rabbits. It is also possible that LHV-4 is present in wild rabbit populations but is not often transmitted to domestic rabbits.[158]

Clinical presentation

The primary lesions are conjunctivitis and periocular swelling, multifocal hemorrhagic/ulcerative dermatitis on the face and dorsum.[154] Clinical signs include progressive weakness, anorexia, respiratory distress, and abortion.[73] Frequently animals are found dead with no previous evidence of disease.

Pathophysiology

Death is due to cardiovascular and respiratory failure.[155]

Diagnosis

At necropsy there is massive necrosis and fibrin deposition within red pulp of the spleen.[73] Large eosinophilic, intranuclear inclusion bodies are observed microscopically in tissue sections of skin, spleen, and lung.[154] Hemorrhagic dermatitis and panniculitis are associated with epidermal microvesicular degeneration, dermal and subcutaneous vascular necrosis, and thrombosis. Other findings include hemorrhagic necrosis of the myocardium with rare intranuclear inclusions within stromal cells, multifocal pulmonary hemorrhage, and hemorrhage with sinus erythrophagocytosis in lymph nodes.[73]

VIRAL INFECTIONS OF LABORATORY SIGNIFICANCE

Astrovirus: Probable Factor in Enteritis Complex

A novel astrovirus (Family: Astroviridae; Genus: *mamastrovirus*) was recently identified by screening rabbits with enteritis complex and healthy rabbits.[160] Rabbit astrovirus was found in 10 (43%) of 23 samples from rabbits with enteric disease and in 25 (18%) of 139 samples from healthy rabbits in Italy during 2005 to 2008. The median titers of virus in the rabbits with enteric disease were 10^3 greater than in the healthy rabbits.

Astroviruses are a family of RNA viruses with 2 genera: *mamastrovirus* and *avastrovirus*. The genus *mamastrovirus* is associated with gastroenteritis in most animal species and humans.[161] Astrovirus infections are regarded as the second most common cause of viral diarrhea in children after rotavirus infection, but in animals, their association with enteric diseases is not well documented, with the exception of turkey and mink astrovirus infection.[161]

The multifactorial enteritis complex of juvenile rabbits[103,105,117] can be caused by bacteria, viruses, and parasites. Several different viruses have been isolated from rabbits with diarrhea, such as rotavirus, coronavirus, and now astrovirus. Whether natural outbreaks of enteritis can be caused by these viral agents alone or in conjunction with other pathogens is not clear. Rabbit astroviruses should be included in the diagnostic algorithm of rabbit enteritis complex. Further experiments to increase information about their epidemiology and potential pathogenic role are required.

Bornavirus: Borna Disease

Borna disease virus (Family: Bornaviridae; Genus: *bornavirus*) (BDV) is the cause of a fatal neurologic disease primarily of horses and sheep that occurs sporadically in central Europe. Incidence is highest during spring and summer. Arthropods have been discussed as a potential vector, but BDV has never been isolated from insects in Europe.[162] A definite virus reservoir for BDV has not been found; various rodents most likely represent such a reservoir.[162] Natural infections in other Equidae, ruminants, rabbits, and cats have also been described in Europe, North Africa, and the Middle East[162,163]; however, the virus exists worldwide. The infection can be fatal, but most carriers are persistently infected without showing clinical signs. Recently, avian bornavirus was identified as the cause of proventricular dilatation disease in parrots, and, like Borna disease virus, has been detected worldwide.[164]

BDV is assumed to be transmitted through salivary, nasal, or conjunctival secretions. Animals become infected by direct contact with these secretions or by exposure to contaminated food or water. A minimum incubation period of 4 weeks is estimated for horses and sheep. In rabbits, natural infections have been reported only in Germany.[163] Clinical signs in naturally and experimentally infected rabbits are neurologic. Although Borna disease is rare in rabbits, the worldwide existence of the virus

means the infection must be differentiated from rabies virus infection and *Encephalitozoon cuniculi* infection.[165] Histopathologically, Borna disease is characterized by a nonpurulent inflammation of the brain and the spinal cord.[166] The detection of BDV in diseased animals, mainly sheep and horses, is achieved by histologic, immunohistochemical, and serologic approaches and/or PCR-based technologies.[167]

Rabies Virus: Rabies

Rabies virus (Family: Rhabdoviridae; Genus: *lyssavirus*) infection is relatively rare in both pet and feral rabbits. Of the 87,700 cases of animal rabies reported in the United States from 1992 to 2002, only 621 occurred in rodents or lagomorphs.[168,169] The majority (559 cases) occurred in groundhogs (*Marmota monax*) and were most likely because of den contact from infected skunks or raccoons.[169] Despite its rarity, rabies has been reported in pet rabbits in Western Europe and North America.[170–174] All cases have been in outdoor-housed pet rabbits. Most cases have come in contact with wildlife carrying rabies (eg, raccoon in North America, fox in Europe) but the source of infection in some rabbits remains unknown.

Both furious and dumb forms of rabies have been reported in naturally infected rabbits; however, the dumb form seems more common. Unilateral pelvic limb paresis or paralysis has been reported as an early clinical sign in domestic rabbits.[171] The one case of furious rabies described the rabbit biting at inanimate objects.[172]

Currently, there is not a rabies vaccine approved for use in rabbits. The only way to prevent rabies infection in rabbits is to prevent exposure. Veterinarians in rabies-enzootic areas should be familiar with the clinical signs of rabies in rabbits and should caution rabbit owners about the need to protect their pets from contact with wildlife.

Vaccinia Virus: Rabbitpox (Rabbit Plague)

Because of its widespread use as a smallpox vaccination in humans, and its wide host range, vaccinia virus (Subfamily: Chordopoxvirinae; Genus: *orthopoxvirus*) sometimes has caused naturally spreading diseases in domestic animals (eg, teat infections of cattle) and also in laboratory rabbits (rabbitpox). Epidemics of rabbitpox occurring in isolated animal rooms were reported in the United States and Netherlands.[175,176]

The disease is acute and rapidly fatal. Confluent papules on the skin, sometimes accompanied by necrosis and hemorrhage, characterize rabbitpox.[177,178] Papular lesions may occur in the oropharynx, respiratory tract, spleen, and liver.[179] In the so-called “pockless” form, a few pocks were present in the oral cavity, and focal hepatic necrosis, pleuritis, and splenomegaly were observed.[180] The primary site for replication in the naturally occurring disease is the respiratory tract.[181] There is a subsequent viremia with replication in lymphoid tissues and skin.[181]

Now that smallpox vaccination has been discontinued for the civilian populations of all countries, rabbitpox is unlikely to be seen. However, the use of aerosolized rabbitpox infection as an animal model for evaluation of antivirals under development for the therapeutic treatment of human smallpox still continues. Consequently, rabbitpox may be seen in laboratory rabbits if the experimental virus is not confined to the biocontainment research area.[182]

Pleural Effusion Disease Virus (Infectious Cardiomyopathy Virus): Pleural Effusion Disease and Cardiomyopathy

Pleural effusion, right-sided heart enlargement, mesenteric lymphadenopathy, and multifocal necrosis of multiple organs have been associated with infection by a coronavirus referred to as pleural effusion disease virus (PEDV) (Family: Coronaviridae; Genus: *coronavirus*) in laboratory rabbits in North America and Europe.[183] PEDV

was discovered as a contaminant of *Treponema pallidum* (the causative agent of syphilis), which is maintained by intratesticular inoculation of laboratory rabbits.[184] PEDV infection is not seen in pet rabbits. Different PEDV isolates vary in pathogenicity and range from subclinical infection to infection causing more than 50% mortality.[185] Lymphoid depletion of splenic follicles, focal degenerative changes in lymph nodes and thymus, proliferative changes in glomerular tufts, and uveitis characterized fatal infections.[183,186] In one infection, multifocal myocardial degeneration and necrosis were seen.[187] Antibodies to 2 human strains of coronavirus have been demonstrated in convalescent rabbit sera and antigen to human 229E coronavirus (one of the 4 human coronaviruses circulating worldwide and a proven common cold virus in healthy adults) was detected in myocardial lesions.[188,189] The evidence suggests that the causative agent is not a natural pathogen of rabbits.

Rabbit Enteric Coronavirus: Coronaviral Enteritis

Rabbit enteric coronavirus (RECV) (Family: Coronaviridae; Genus: *coronavirus*) induces disease in juvenile rabbits that is characterized by intestinal villus attenuation, malabsorption, and diarrhea. Infection may predispose rabbits to, or be obscured by, the enteritis complex. Although RECV has been isolated, it has not been characterized.[190]

Coronavirus-associated enteritis has been reported in commercial rabbitries but generally with low mortality.[191] In one report, an outbreak of fatal enteritis in 3 to 8-week old rabbits occurred in a barrier-maintained breeding colony in Germany.[192] The prevalence of detectable antibody in a serologic survey of North American commercial rabbitries ranged from 3% to 40%.[193] The presence of coronaviral particles in feces of young diarrheic rabbits indicates the virus may play a role in enteritis complex. However, coronaviral particles have also been observed in gastrointestinal contents of healthy rabbits. Differential diagnoses include *E coli* infections, coccidiosis, rotavirus infection, and clostridial enteropathies.

Experimentally and naturally infected young rabbits may be emaciated and dehydrated and show perineal fecal staining.[192,194] The cecum may be distended, with a milky to tan liquid.[192,194] Microscopic changes are confined to the small and large intestines.[194] Distinctive findings include villous blunting, vacuolation and necrosis of enterocytes, mucosal edema, and polymorphonuclear and mononuclear cell infiltration.

Confirmation of diagnosis requires demonstration of coronaviral particles from gastrointestinal contents by electron microscopy.[190] The virus has not been grown in cell culture.

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