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MICROBIOLOGY

Viral diseases of sheep in Brazil: a review and current status

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ABSTRACT: The increase in sheep production is directly related to the health status of the flock. Brazil is one of the largest sheep producers in the world, and the sheep flock is concentrated in southern and northeast regions. Infectious diseases are responsible for severe economic losses resulting from a decrease in milk and meat production, deaths, and cost of treatment. Among infectious diseases, viral diseases are described chiefly in case reports or retrospective studies. This study aimed to review the main features of viral diseases that affect sheep in Brazil and their current situation in the Brazilian territory. We included eight viral diseases described in Brazil: rabies, bluetongue, contagious ecthyma, foot and mouth disease, visna-maedi, enzootic nasal tumor, ovine pulmonary adenocarcinoma, and border disease. We review the etiological, epidemiological, clinical, and pathological findings for each agent and included differential diagnoses, information on recommended diagnostic methods to confirm the disease etiology, and control measures. This study served as quick consultation material for field veterinarians for an accurate diagnosis.
Key words: virology, pathology, ovine, diagnosis, Brazil.

Doenças virais em ovinos no Brasil: revisão e status atual

RESUMO: O aumento da produção ovina está diretamente relacionado ao status sanitário do rebanho. O Brasil é um dos maiores produtores mundiais de ovinos, e o rebanho está concentrado nas regiões nordeste e sul do país. As doenças infecciosas são responsáveis por perdas econômicas severas que resultam da diminuição na produção de leite e carne, mortes e custos com tratamentos. Entre os agentes infecciosos, as doenças de origem viral são, em sua maioria, descritas em relatos de caso ou estudos retrospectivos. Este estudo teve como objetivo revisar as principais características das doenças virais que afetam ovinos no território brasileiro, e qual sua situação atual. Nós incluímos oito doenças virais diagnosticadas no Brasil: raiva, língua azul, ectima contagioso, febre aftosa, maedi-visna, tumor enzoótico nasal, adenocarcinoma pulmonar ovino, e pestivirose. Revisamos os achados etiológicos, epidemiológicos, clínicos e patológicos de cada agente e incluímos seus respectivos diagnósticos diferenciais, informações acerca dos métodos diagnósticos para confirmação da etiologia da doença e medidas de controle e prevenção. Esse estudo tem o propósito de servir como objetivo servir de material de consulta rápida, especialmente para veterinários de campo realizar um diagnóstico acurado.
Palavras-chave: virologia, patologia, ovino, diagnóstico, Brasil.

INTRODUCTION

Sheep farming in Brazil has been practiced since the colonization and snowballed in recent years. The national flock is the 8th largest flock worldwide with approximately 18 million sheep and is concentrated primarily in southern and northeastern regions, where environmental and climatic conditions are favorable for sheep production (FAO, 2012; HERMUCHE et al., 2013; EMBRAPA, 2016). The Northeast region has 56% of the Brazilian sheep while the South has 32% and the Southeast is third with 3.4% (IBGE, 2006). Even with this flock size, production still tends to be informal, and there is an evident deficiency in the national availability of sheep products, with insufficient production and a trading volume that does not support the industrialization of lamb (XIMENES & CUNHA, 2012).

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The development of sheep production is directly related to flock health. In Brazil, infectious diseases are associated with 33 to 39% of all causes of death in sheep (RISSI et al., 2010b; ALMEIDA et al., 2013; CECCO et al., 2021). Of these, viral diseases are described chiefly in case reports or retrospective studies. Complete studies of the epidemiological, clinical, and pathological features and diagnostic approaches for these diseases are limited in the literature. This research reviews the available literature on viral agents related to clinical disease in sheep in Brazil. We compile the clinical, pathological, and laboratory findings for each agent, and included differential diagnoses and information on recommended diagnostic methods to confirm the disease etiology. We also present the current situation of these viral diseases in the national territory.

MATERIALS AND METHODS

Peer-reviewed scientific papers (original research, case reports, and reviews) of viral diseases of sheep were searched in electronic databases, such as SciELO, Medline, PubMed, Web of Science, Scopus Google Scholar, MEDLINE, Latindex, BASE, and WorldWideScience. Search terms sheep, ovine, disease, viral, virology, and viruses names were used during the search were entered into the NCBI-PubMed and Google Scholar databases one by one. The title, abstract, methodology, and/or supplementary information associated with the research articles that emanated from the online database searches up to July 2022 were screened for relevance for inclusion in our study. There were no restrictions regarding the year of publication (last search performed in July 2022) or language (Spanish, Portuguese, and English). Conference abstracts, bachelor, master, and Ph.D. documents were not considered. A further search for additional epidemiological data on confirmed viral diseases in sheep between 1999 and 2019 were accessed at the Painel de Consultas de Dados de Doenças from the Sistema Nacional de Informação Zoossanitária (BRAZIL, 2021). Based on the consistent epidemiological, clinical, and pathological characterization report in the literature, we selected eight diseases (rabies, bluetongue, contagious ecthyma, foot and mouth disease, visna-maedi, enzootic nasal tumor, ovine pulmonary adenocarcinoma, and border disease) (Table 1). This review did not include diseases that were not well-characterized or had no confirmatory tests. We have emphasized naturally-occurring viral infections that cause clinically significant disease.

All figures used in this manuscript were taken by the authors during cases or outbreaks of viral diseases, with the exception of foot and mouth disease.

Viral agents

Rabies

Etiology and epidemiology

Rabies is an infectious, fatal disease of wild and domestic animals caused by the rabies virus (RABV), a neurotropic virus member of the family *Rhabdoviridae* and genus *Lyssavirus*. Rabies viruses are enveloped, bullet-shaped, single-stranded, negative-sense RNA viruses with approximately 180 to 200 nm in length and 80 nm in diameter (CALLAN & VAN METRE, 2004). The lyssaviruses are classified into seven genotypes (BOURHY et al. 1993). Genetic and antigenic variation is observed within the classic rabies viruses, which belong to genotype 1. This variation is related to reservoir species and the geographic location of the rabies virus isolate. However, there is antigenic homology between these classic rabies virus isolates (CALLAN & VAN METRE, 2004).

In a molecular study performed in Southern Brazil, the sequencing of RABV was made targeting the nucleoprotein gene (N) amplification. The phylogenetic tree showed three clusters. The cluster 1 corresponded to sequences of viruses recovered from vampire bats (*D. rotundus)*; and at least two sublineages (1A and 1B) of RABV has been shown to be circulating in Brazil. Subcluster 1A included isolates from several regions of Brazil (the Southeast and North) and from Ecuador. In subcluster 1B along with isolates from Southern Brazil, sequences corresponding to viruses recovered from GenBank isolated from Uruguay and Argentina were grouped together. Also, sublineage 1A seems to have a wider geographic distribution than sublineage 1B (FERNANDES et al., 2020).

Due to the zoonotic profile and mortality rates of 100%, this is a disease of major importance for public health. The RABV is primarily transmitted to herbivores through the bite of an infected animal, commonly bat vampire *Desmodus rotundus* in South and Central America (CALLAN & VAN METRE, 2004; CANTILE & YOUSSEF, 2016). After an initial replication in myocytes near the bite, viral particles invade the local neuromuscular junction and ascend to the paravertebral ganglia and central nervous system via axoplasmic flow. A protein present in the RABV viral envelope, the RABV glycoprotein, is mainly responsible for neurotropism by binding to many neural tissue receptors (CANTILE & YOUSSEF, 2016).

Table 1 - Infectious viral diseases in sheep in Brazil.

Disease	Main Clinical Signs	Main Gross Findings	Main Histopathological Findings	Tissues to be Submitted to Virology
Rabies	Incoordination, opisthotonus, and convulsion (acute disease)	Unremarkable	Nonpurulent meningoencephalitis and meningomyelitis with ganglioneuritis and intracytoplasmic neuronal inclusion body	Brain samples from dead animals
Bluetongue	Respiratory distress, and fever (acute disease)	Severe pulmonary edema, hemorrhages, and ruminal content in nasal cavity, trachea and bronchi	Myonecrosis of the esophagus, heart, and skeletal muscle	Blood from live animals; lung, spleen, lymph nodes, brain, bone marrow, and liver samples from dead animals
Contagious ecthyma	Scabs in the lips and nose and anorexia (acute disease)	Papules, ulcers, and scabs at oral commissures, lips, and nose	Intracorneal vesicles, epithelium hyperplasia, and areas of epidermal ulceration	Scab material of papular lesions from live or dead animals
Foot and mouth disease	Lameness, anorexia, and fever (acute disease)	Loss of body condition and ulcerative lesions on the mouth, interdigital space, teats, vulva, and prepuce	Necrosis of the epithelium, with neutrophilic infiltrate and vesicle formation	Epithelial tissue of vesicles, heparinized blood, esophageal–pharyngeal samples, and milk from live or dead animals
Visna-maedi	Respiratory distress, ataxia, mastitis, and arthritis (chronic disease)	Heavy non-collapsed lung and softening of the periventricular white matter of the brain	Formation of lymphoid follicle-like structures in the lung, choroid plexus, and mammary gland	Serum from live animals; blood, lung, brain, mammary gland, and synovial capsule samples from dead animals
Enzootic nasal tumor	Respiratory distress, seromucoid nasal discharge, and progressive weight loss (chronic disease)	Tumor in the nasal cavity	Nasal adenocarcinoma	Tumor samples from dead animals
Ovine pulmonary adenocarcinoma	Respiratory distress and abundant frothy secretion draining from the nostrils (chronic disease)	Heavy non-collapsed lung, with a large amount of fluid and raised grey nodules	Bronchioloalveolar adenocarcinoma	Bronchoalveolar lavage samples from live animals; lung tissue samples from dead animals
Border disease	Weak lambs with conformation deformities, abortion, and stillbirths	Arthrogryposis, cerebellar dysplasia, hydranencephaly, and porencephaly	Cellular disorganization in the cerebellar cortex, reduction of the granular layer of the cerebellum, and hypomyelinogenesis	Heparinized blood samples from live animals; thyroid, kidney, brain, spleen, gastrointestinal tract, and lymph nodes samples from dead animals

Rabies has a nearly worldwide distribution. Few geographically isolated locations are currently free of enzootic rabies, including Antarctica (WHO, 2021). Natural infection in animals by the RABV has been documented in Brazil since 1892 (BRAZIL, 1988). Any suspected case must be notified immediately to the authorities (BRAZIL, 2013). Unlike in cattle, rabies is uncommon in sheep in the national territory (RISSI et al., 2008; BASSUINO et al., 2016). In retrospective studies of diseases diagnosed in sheep, the frequency rate of rabies is 0.6%-1.1% of all diseases and 3.1% of all neurological diseases (RISSI et al., 2010a; RISSI et al., 2010b; ALMEIDA et al., 2013). Only 257 individual cases have been officially confirmed in sheep from several Brazilian states over the past two decades (Figure 1) (BRAZIL, 2021). This low frequency is associated with the control of the urban rabies cycle in the national territory, and rare attacks by vampire bats on sheep, due to thick wool cape in the sheepskin (LIMA et al., 2005; RISSI et al., 2008).

Clinical and pathological findings

The incubation period of rabies typically ranges between 30 and 90 days and is related to the distance of the initial inoculation site from the CNS

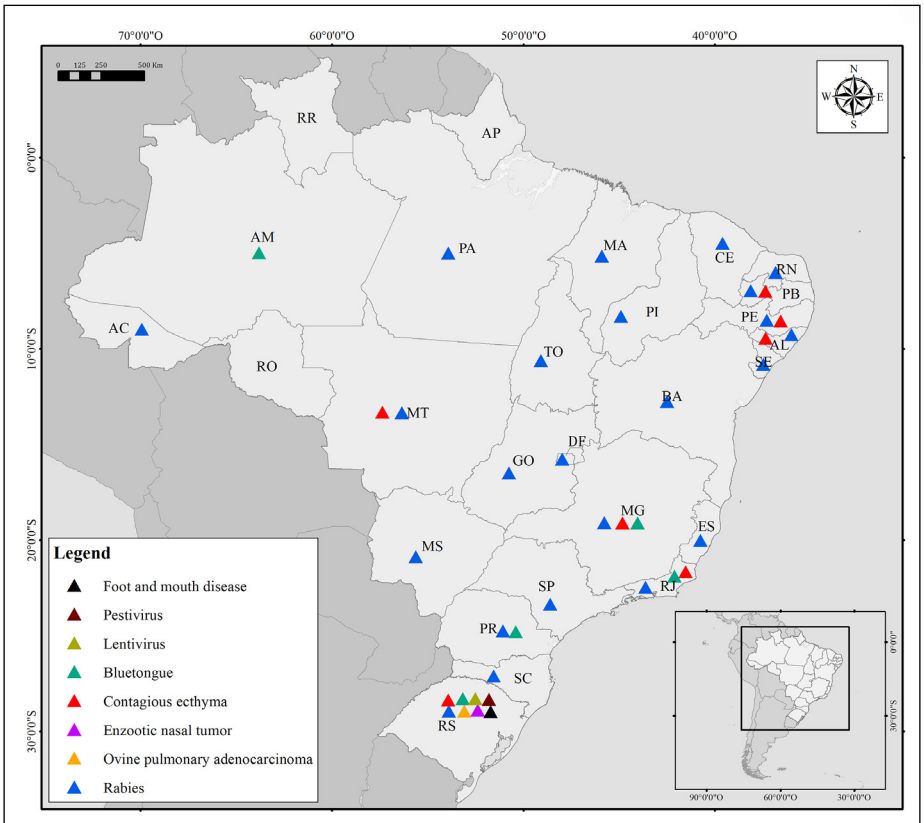

Figure 1 - Infectious viral diseases in sheep in Brazil between 1999 and 2019.

(BAER, 1990). The clinical course of rabies is usually acute, from 1-2 days, but can last up to 10 days. Clinical signs between domestic species can vary and include fever, decreased appetite, paresthesia, ataxia, altered mentation, paralysis, and coma (BAER, 1990). In sheep, RABV commonly develops the paralytic form of the disease, characterized by a gradually ascending ataxia and paresis and paralysis of the limbs (BAER, 1990; RISSI et al., 2010b; BASSUINO et al., 2016). However, sheep can be aggressive in a few cases and present head tremors, salivation, and hyperexcitability (RIET-CORREA et al., 1983). Death generally occurs within 1-2 days after recumbency and is caused by respiratory failure (BAER, 1990).

While specific gross lesions are absent at postmortem examination, self-inflicted wounds consistent with recumbency and agonal convulsions, aspiration pneumonia, and fully distended urinary bladder are described in infected sheep (BAER, 1990; BASSUINO et al., 2016). Generally, the severity of histological lesions reflects the duration of clinical disease (BAER, 1990). Especially in sheep, the neurological lesions are distributed mainly in the spinal cord, brainstem, thalamus, and cerebellum (BASSUINO et al., 2016). Histological lesions are characterized by nonsuppurative meningoencephalomyelitis, with vessels with cuffing lymphocytes, formation of microglial nodules, neuronal degeneration, gliosis of gray matter (Figure 2A), and infiltration of leptomeninges by lymphocytes. Ganglioneuritis may be present and is characterized by acute degeneration of ganglion cells, neuronophagia, formation of *Nageotte* nodules, and lymphocytic infiltration (Figure 2B) (CANTILE & YOUSSEF, 2016). In sheep, the infiltration of lymphocytes in the neurohypophysis has been described (RISSI et al., 2010b). Intracytoplasmic acidophilic inclusion bodies in neurons, called Negri bodies, are most observed in the spinal cord (Figure 2C) (BASSUINO et al., 2016).

Diagnosis

The official diagnosis of rabies in Brazil consists of a direct fluorescent antibody test (DFAT)

on fresh CNS samples, posteriorly confirmed by biological tests (inoculation of the sample in mice or cells) (SWANEPOEL, 2004; BRAZIL, 2009). The current recommendation for the collection is to send refrigerated or frozen fragments of the cerebrum, cerebellum, thalamus, and cervical spinal cord for RABV detection by DFAT. The remaining CNS and other organ fragments must be fixed in 10% neutral buffered formalin and submitted to histological evaluation (BRAZIL, 2009). Although, unofficial, immunohistochemistry (IHC) is also a valuable tool for confirming cases where there is not an available refrigerated brain sample (Figure 2D) (RISSI et al., 2010b; BASSUINO et al., 2016). Although is not officially used for routine, real-time RT-PCR can be employed in diagnosing rabies (FERNANDES et al., 2020).

Prevention and control

Rabies is a zoonotic disease with an important impact on public health; therefore, multiplex strategies are required for rabies control in animals and humans. The epidemiological surveillance of rabies involves the estimation of the incidence and prevalence of the disease in a geographical region (SWANEPOEL, 2004). These data provide the base for planning control measures, such as vaccination implementation and control of rabies in wildlife, including the elimination of reservoir species. Since in Brazil, the distribution of livestock cases is frequently related to the presence of *Desmodus rotundus* populations, the main reservoir and source of infection for livestock, the identification of these species foci is essential to determine where control measures must be implemented (FERNANDES et al., 2020).

Bluetongue

Etiology and epidemiology

Bluetongue virus (BTV) is a non-enveloped with an icosahedral organization arbovirus, member of the *Reoviridae* family, genus *Orbivirus* (MERTENS et al., 2004). The viral genome comprises ten segments of double-stranded RNA encoding for non-structural proteins (NS1 – NS4), and seven structural proteins (VP1 – VP7). Segment-2 (Seg-2) encodes the outer-capsid protein, VP2, the most variable BTV protein. The VP2 contains most of the epitopes that interact with neutralizing antibodies and is the main determinant of the virus serotype (HUISMANS & ERASMUS, 1981). BTVs are characterized by a remarkable genetic diversity, with differences in virulence between

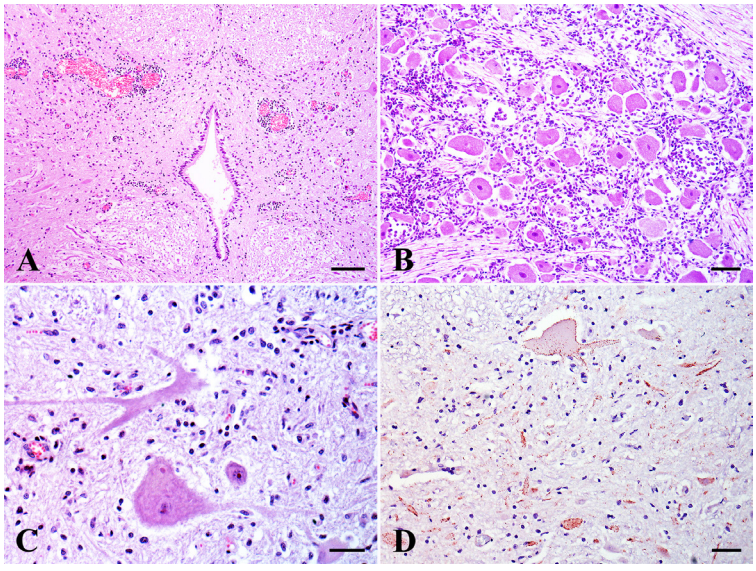

Figure 2 - Rabies – A. Marked multifocal lymphoplasmacytic perivascular cuffs with multifocal gliosis. H&E stain; bar = 200 µm. B. Ganglioneuritis is characterized by severe infiltrate of lymphocytes in the ganglia, neuronophagia with Nageotte nodules. H&E stain; bar = 100 µm. c. Inclusion body in the perikarium of a neuron (Negri's inclusion body). H&E stain; bar = 50 µm. d. Strong granular labeling of the neuronal perikaryum. IHC; bar = 100 µm.

serotypes and viral strains (MACLACHLAN, 1994; CONSTABLE et al., 2017). Currently, 27 different BTV serotypes that infect ruminants have been described, mainly in Europe, United States, Australia, and South Africa (MACLACHLAN et al., 2009; MAAN et al., 2012; JENCKEL et al., 2015).

South America has the ideal climatic conditions for the survival and proliferation of *Culicoides* spp., the main vector of arboviruses. Serological investigations indicate the spread of BTV over the continent since 1978 (LOBATO et al., 2015). The weather conditions are a major risk factor for the occurrence of BT because it is a vector-dependent disease. Areas with high temperatures and humidity are favorable for the development of mosquito larvae (MACLACHLAN, 1994; CONSTABLE et al., 2017). Therefore, in temperate zones (epidemic areas), including the southern states of Brazil, the outbreaks are often seasonal and usually occur during summer or early autumn (MACLACHLAN, 1994; RIET-CORREA, 2007).

Although BT can affect wild and domestic animals, sheep are the domestic species most susceptible. BTV serotypes described in sheep in Brazil include the serotype 4 in the Rio de Janeiro, Minas Gerais, and Rio Grande do Sul (RS) states (BALARO et al., 2014; LIMA et al., 2016; GUIMARÃES et al., 2017); serotype 12 in the Paraná and RS states (CLAVIJO et al., 2002; ANTONIASSI et al., 2010b); and serotypes 1, 4, and 17 in the RS state (BIANCHI et al., 2017; GUIMARÃES et al., 2017). BT cases without determined serotypes are reported in the Amazonas State (BRAZIL, 2021). Currently, veterinarians are instructed to immediately notify any suspected cases (BRAZIL, 2013). Between 1999 and 2019, a total of 406 individual cases have been officially confirmed in sheep in Brazil (BRAZIL, 2021). The morbidity and mortality rates can vary significantly among outbreaks (MACLACHLAN et al., 2009). When the virus is introduced for the first time in a flock, the flock is considered naive, and the morbidity may reach 50-75% and the mortality 20-50% (CONSTABLE et al., 2017; RIET-CORREA, 2007). However, typically the mortality rate rarely exceeds 30% (MACLACHLAN et al., 2009) and the lethality rate can reach 21.7% (BIANCHI et al., 2017).

Clinical and pathological findings

BTV pathogenesis results from viral replication in endothelial cells, causing cell injury and necrosis and leading to vascular thrombosis, tissue infarction, and hemorrhage (MACLACHLAN et al., 2009; BIANCHI et al., 2017). Clinical signs include mainly anorexia, lethargy, fever, condition loss, serous to bloody nasal discharge admixed with ruminal content (Figure 3A), with occasional formation of crusts around the nares, facial swelling, respiratory distress, hyperemic or cyanotic oral mucosa, swollen and cyanotic tongue, oral erosions and ulcers, lameness with hyperemia of the coronary band, and weakness (MACLACHLAN et al., 2009; BIANCHI et al., 2017). Death occurs after a clinical course of 3 to 7 days (BIANCHI et al., 2017).

Grossly, hyperemia, hemorrhages, erosion, and ulceration of the upper gastrointestinal tract mucosa can be observed (Figure 3B). Hyperemia and plant fiber materials mixed with foamy liquid can be found in the nasal cavity and trachea. Characteristic lesions include hemorrhages in the pulmonary artery (Figure 3C) and white and firm areas in the skeletal and cardiac muscle, mainly in the esophagus and in the papillary muscle of the left ventricle (MACLACHLAN et al., 2009). In the esophagus, mild dilation and sagging associated with hemorrhage are observed (GUIMARÃES et al., 2017). In some cases, abundant ingesta collects in the lumen of this organ, forming a mold that stretches and markedly distends it (Figure 3D) (ANTONIASSI et al., 2010a). Other lesions include hemorrhages within the subcutis, pleural, and/or pericardial effusion (MACLACHLAN et al., 2009). The lung is usually not collapsed and shows elastic consistency and abundant amounts of foamy liquid (Figure 3E) (GUIMARÃES et al., 2017). In cases in which aspiration pneumonia can occur concomitantly, multifocal consolidation areas predominantly in the cranioventral region of the lung associated with plant fiber material in the bronchi are observed (ANTONIASSI et al., 2010a; GUIMARÃES et al., 2017).

The main histological feature is myonecrosis of the esophagus, heart, and skeletal muscle, characterized by eosinophilic myofibers with rounded edges in cross-section, sometimes hypercontracted and segmented with loss of striations (Figure 3F). The necrosis is frequently surrounded by inflammatory infiltrate of macrophages (ANTONIASSI et al., 2010a; GUIMARÃES et al., 2017). Pulmonary edema is frequent and is one of the characteristics of fatal BTV infection (MACLACHLAN et al., 2009). Several cases of BT are associated with aspiration pneumonia (ANTONIASSI et al., 2010a). In these cases, the lesions observed include fibrinosuppurative bronchopneumonia with alveoli, bronchioles, and bronchi filled by intact and degenerate neutrophils and fibrin, vegetable fibers, and intralesional bacterial aggregates (ANTONIASSI et al., 2010a; BIANCHI et al., 2017). On the gastrointestinal tract, erosion and ulceration of the lining epithelium with vacuolar

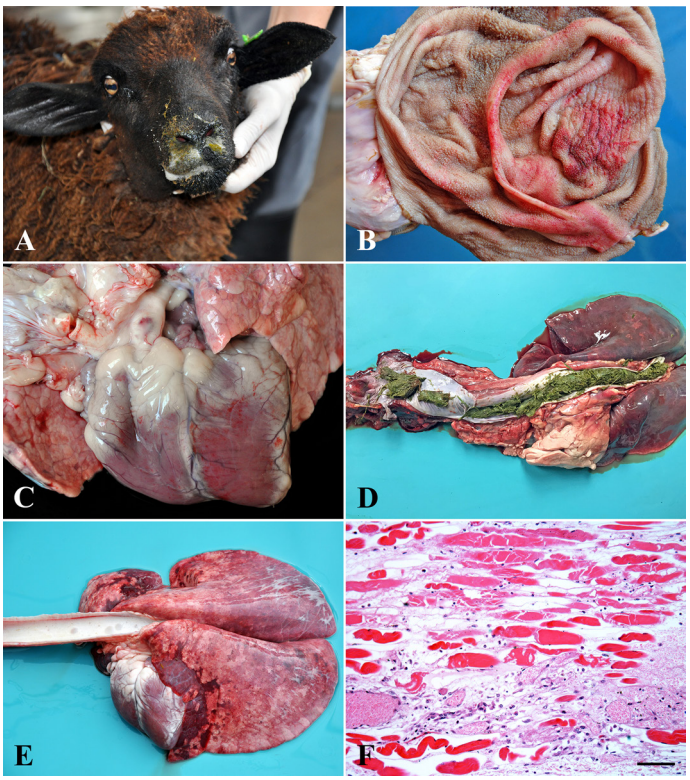

Figure 3 - Bluetongue – A. Abundant greenish mucous nasal discharge. Note the marked facial swelling, mainly on the upper lip. B. Rumen. Multifocal hemorrhages and erosions on rumen pillars and reticulum mucosa. C. Hemorrhages in the pulmonary artery. D. Large amounts of ingesta dilating the esophagus, which acquired the anatomic form of the organ. E. Lung and trachea. Increased, not collapsed, heavy, reddened, and shiny lung, with the rib impressions. In the trachea, there is a moderate amount of foamy content (edema). F. Photomicrograph of a section of the esophagus. The muscular layer of the esophagus presents severe multifocal to coalescing hyaline and flocculate degeneration and necrosis, with mild inflammatory infiltrate of macrophages and edema. H&E stain; bar = 200 µm.

degeneration of adjacent epithelial cells are observed, frequently covered by fibrin, intact and degenerate neutrophils, erythrocytes, and cell debris (BIANCHI et al., 2017). The congestion, edema, and hemorrhages observed grossly are a direct consequence of the virus-mediated vascular injury, represented histologically by endothelial hypertrophy with perivascular edema, hemorrhage, and infiltration of lymphocytes and macrophages. Thrombosis is also commonly observed (MACLACHLAN et al., 2008; 2009).

Diagnosis

The presumptive diagnosis of BTV is usually based on clinical, pathological, and epidemiological findings. The confirmation of the diagnosis is made by isolating the virus through cell cultures, inocula, or embryonated eggs, by identifying the agent through virus-neutralization (VN); or by detecting specific antibodies. Techniques for detecting the virus are immunofluorescence, competitive ELISA (c-ELISA) which is highly sensitive for antigen detection, real-time RT-PCR, multiplex PCR for BTV RNA detection, and the sequencing technique to obtain the complete genomic sequence of BTV, which can be useful for classification into serogroup, serotype, and topotype. The ELISA test is highly specific and sensitive to detect antibodies to BTV strains and serotypes (ROJAS, 2019).

Prevention and control

Although, several outbreaks of bluetongue with large economic losses have happened in Brazil in the last decade, no contingency plans are established. Among preventive measures to control the introduction of BTV is the restriction of introducing sheep without performing viral isolation or PCR assay from blood samples. Sheep without previous testing must be submitted to quarantine and present negative results in order to obtain a health certificate (RADOSTITIS et al., 2007, ALFIERI et al., 2012, MACLACHLAN; MAYO, 2013). Also, the reduction of the vector population using insecticides has been described as a preventive measure, but can be impractical for routine due to the high cost. Vaccination is a preventive measure most used in countries where BT is an important sanitary problem. However, in Brazil, there are no licensed vaccines (ALFIERI et al., 2012; BALARO et al., 2014).

Contagious ecthyma

Etiology and epidemiology

Contagious ecthyma (CE), also known as contagious pustular dermatitis or scabby mouth, is caused by an Orf virus, is a double-stranded DNA virus of the family *Poxviridae*, genus *Parapoxvirus* (PPV), and its viral genome is one of the smallest in Poxviridae family (MAZUR et al., 2000). This genus is composed of antigenic and genetically related viruses that present similar morphology and virulence factors: Orf virus (ORFV), bovine papular stomatitis virus, pseudocowpox virus, and parapoxvirus of red deer in New Zealand (FLEMING et al., 1993). ORFV is the prototype of PPV and is the etiological agent of CE, a severe exanthematic dermatitis that affects domestic and wild ruminants (MAZUR et al., 2000; ABRAHÃO et al., 2009) and is considered an occupational zoonosis (CONSTABLE et al., 2017). There are viral isolates derived from different animal hosts as well as viral isolates from the same host species that originated from different geographical locations. However, few studies are available on Brazilian parapox virus isolate (MAZUR et al., 2000).

Typically, CE occurs in late summer, fall, and winter on pasture and in feedlots. Lambs are more susceptible to disease than adults (NANDI et al., 2011). The disease transmission occurs through contact between infected and susceptible animals or via environmental contamination (NETTLETON et al., 1996). Iatrogenic transmission of the ORFV can also occur during minor or major surgical intervention, hand contact, drenching, and ear tagging (ALLWORTH et al., 1987).

In the last years, CE outbreaks have occurred worldwide (ABRAHÃO et al., 2009) and the disease is endemic in Brazil, with heterogeneity among Brazilian viral isolates (MAZUR et al., 2000; ABRAHÃO et al., 2009). Confirmed cases must be reported monthly to the authorities (BRAZIL, 2013). Several reports demonstrate the virus circulation in Brazilian territory, including outbreaks of the clinical disease in Southern states including Rio Grande do Sul (SALLES et al., 1992, PANZIERA et al., 2016), Brazilian semiarid states including Paraíba, Alagoas, and Pernambuco (MACÊDO et al., 2008; NÓBREGA et al., 2008), Midwest states including Mato Grosso (ABRAHÃO et al., 2009), and Southeast states including Minas Gerais and Rio de Janeiro (MAZUR et al., 2000; BALARO et al., 2014). Unfortunately, data from individual cases in Brazil over the past two decades are not available.

The most effective way for the ORFV to enter a new area is by introducing infected animals. Orf virus is robust in a dry environment and can survive for months or even years, but its lifespan may be shorter in cold and wet conditions. The virus remains viable on the wool of recovered animals for substantial periods (NANDI et al., 2011). CE is not usually fatal; however, it is considered a debilitating condition that can be fatal, especially in lambs prevented from suckling or succumbing to secondary bacterial or fungal infections (HAIG & MCINNES, 2002). The morbidity can reach up to 100% after the viral introduction to a naive flock, while mortality may reach 15% and is usually caused by secondary infections and pneumonia (GUMBRELL & MCGREGOR, 1997; CONSTABLE et al., 2017). In enzootic areas, only the lambs develop the disease at the time they begin to change the food from milk to grass. In the summer, myiasis can be a complication of the lesions (HOUSAWI & ABU ELZEIN, 2000). A common consequence of mucosal lesions disrupting the oral epithelium, especially in ORFV-affected lambs, is a secondary bacterial infection (REID & RODGER, 2007).

Clinical and pathology findings

ORFV penetrates through skin lesions/disruptions and replicates in epidermal cells. After the incubation period, which varies from 4 to 8 days, animals present an initial rise in temperature, swollen face (Figure 4A), and develop papules and pustules, surrounded by hyperemia, often at oral commissures and skin of lips and nose. These lesions are followed by thick, tenacious scabs covering a raised area of ulceration, granulation, and inflammation (Figure 4B) (NANDI et al., 2011; PANZIERA et al., 2016). In

lambs, lesions on gingiva adjoining incisors, lateral and dorsal zones of the tongue, and palate are characterized by single or multiple coalescing papules followed by ulceration covered with yellowish exudate (MCELROY & BASSETT, 2007). The disease usually runs for 3–4 weeks. Sheep with extensive lesions can develop anorexia and even starvation, especially in lambs, due to restricted suckling and grazing, since CE lesions are painful (MAZUR et al., 2000; CHAN et al., 2007; ABRAHÃO et al., 2009). Depending on the location, animals can be unwilling to nurse, eat, or walk (NANDI et al., 2011). In humans, ORF usually causes a single skin lesion or a few lesions of a small firm, red to blue papule on a finger, hand, or other exposed part of the body. In some cases, other symptoms include pain, fever, and pruritus. In uncomplicated cases, the lesion heals spontaneously in 3 to 6 weeks (Figure 4C) (NANDI et al., 2011).

Grossly, the skin lesions on the lips and nose are multifocal to coalescing, ulcerated, broad-based, frequently hairless, and malodorous (NANDI et al., 2011; PANZIERA et al., 2016). During the lesion regression, granulomatous lesions can be observed. In some cases, necrotic foci and ulcers can be found on the tongue, gum, pharynx, rumen, and abomasum because of secondary infection. In long-standing clinical cases, the lesions become chronic and progress to proliferative stomatitis, with pseudo-papillomatous growths in the affected areas comprised of epithelial hyperplasia and granuloma formation that can persist for several months (REID & RODGER, 2007). In the advanced stage of the disease, the affected animals can die due to the development of pneumonia (NANDI et al., 2011). The venereal form of ORFV is manifested by the appearance of papules, vesicles, proliferative lesions, and ulcers on the skin and mucosa junction of the vulva of ewes and scrotum, preputial orifice, and penis of rams (DE LA CONCHA-BERMEJILLO et al., 2003).

Histological changes depend on the stage of lesion development (NANDI et al., 2011). Initially, epithelium shows hyperplasia with swollen degenerated cells and eosinophilic cytoplasmic inclusion bodies; however, it is not a consistent feature. The epithelium shows hyperplasia with prominent rete ridges and marked parakeratotic and orthokeratotic hyperkeratosis. The altered epidermis contains intracorneal vesicles or multifocal areas of ulceration covered by serocellular crusts. Keratinocyte degeneration is associated with inflammatory infiltrate of macrophages, lymphocytes, and neutrophils (Figure 4D) (NÓBREGA et al., 2008; NANDI et al., 2011; PANZIERA et al., 2016).

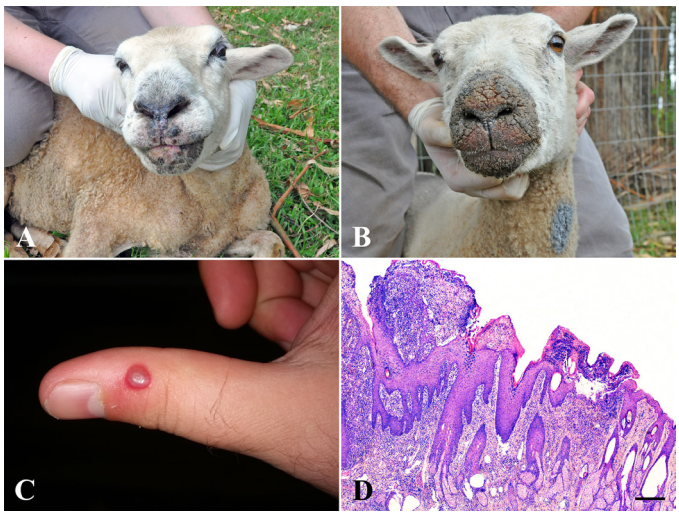

Figure 4 - Contagious ecthyma – A. Bilateral facial swelling, more evident in the nasal plane. B. Severe extensive bilateral proliferative and necrotizing cheilitis and dermatitis of the nasal plane and adjacent facial skin, with crusting, hyperpigmentation, edema, and swelling of the facial region resulting in partial obstruction of the nostrils. C. Violaceous erythematous lesion with a red outer ring and erythematous border in a human finger. D. Severe proliferative and necrotizing dermatitis with serocellular crusting, epidermal hyperplasia, severe intraepithelial neutrophilic infiltrate, ballooning degeneration of keratinocytes. H&E stain; bar = 200 µm.

Diagnosis

The diagnosis of CE is based on clinical and pathological features of characteristic lesions on the anatomic areas of predilection and viral identification. Scab materials collected from papular lesions and serum from affected sheep are usually used to perform viral identification. A variety of laboratory techniques are available for viral identification including transmission electron microscopy, serology, PCR, cell culture isolation, virus neutralization, complement fixation test, ELISA, Western blot, and restriction fragment length polymorphism, but PCR based on B2L or VIR gene followed by Sanger sequencing of the amplification product is the more usual test nowadays to diagnose the parapoxvirus infections (DELHON et al., 2004; GUO et al., 2004; KOTTARIDI et al., 2006; NANDI et al., 2011). Also, qPCR based on B2L gene can be useful to quantify the number of virus particles in the clinical samples (KOTTARIDI et al., 2006). The analysis of B2L gene of Brazilian ORFV isolates revealed a high degree of *nt* similarity among viruses from sheep and goats regardless of the geographical origin. A few *nt* changes were observed more consistently in goat sequences, which may help in identifying the species origin of field viruses (SCHMIDT et al. 2013).

Prevention and control

The eradication of CE once it has entered the flock is difficult, and preventive measures are therefore highly indicated (NÓBREGA et al., 2008). Vaccination is very efficient and is a good cost-effective method of preventing orf virus infections. However, other disinfection practices and measures can be implemented to assist in the control of CE. Two of the most important strategies are the isolation of infected animals to prevent the spread of the disease, and the implementation of quarantine before introducing new animals to the flock, therefore, preventing the entrance of the virus. It is also necessary to be aware that infected equipment can spread the disease, making the appropriate cleaning of these fomites (NANDI et al., 2011; PANZIERA et al., 2016).

Foot and mouth disease

Etiology and epidemiology

Foot and mouth disease (FMD) is caused by an *Aphthovirus* of the *Picornaviridae* family. The virion is non-enveloped and has icosahedral symmetry, with a core of single-stranded RNA containing approximately 8,400 nucleotides (ALEXANDERSEN et al., 2003; DONALDSON & SELLERS, 2007). The virus consists of four structural proteins (VP1-4), and eight non-structural proteins (NSPs; L, 2A, 2B, 2C, 3A, 3B, 3C, and 3D); many factors are determinants of infection and immunity inherent in the molecular constituents of the VP1 protein (ALEXANDERSEN et al., 2003). Described serotypes of FMD, with indistinguishable clinical signs, include types O, A, C, Southern African Territories (SAT) 1, SAT 2, SAT 3, and Asia 1, however, only three of them have been reported in South America (O, A, and C) (MALIRAT et al., 2007). Moreover, within a serotype a wide range of strains may be found, and there is no cross-protection between serotypes (KITCHING, 1998).

FMD is one of the most highly contagious diseases in animals or humans, and the virus rapidly replicates and spreads within the infected animal, among in-contact susceptible animals, and by aerosol (GRUBMAN & BAXT, 2004). Silent dissemination of virus before clinical signs is more probable from infected sheep since sheep excrete a large proportion of virus in one- or two-day period before the occurrence of clinical signs (ALEXANDERSEN et al., 2002; HUGHES et al., 2002). It is the most important disease constraint to international trade in livestock and animal products (DONALDSON & SELLERS, 2007). FMD is a notifiable disease in most countries, and investigations after the first reports are carried out by the official veterinary service (DONALDSON & SELLERS, 2007). Any suspicion of FMD cases in the Brazilian territory must be reported immediately to the appropriate authorities (BRAZIL, 2013).

The disease affects domestic cloven-hoofed animals, including cattle, swine, sheep, and goats, as well as more than 70 species of wild animals (COETZER et al., 1994). FMD is endemic in large areas of Africa, Asia, and South America, and outbreaks have been described in the United Kingdom in 2001 and in Japan and South Korea in 2000 (KNOWLES et al., 2001; ALEXANDERSEN et al., 2003). Only three outbreaks of FMD in sheep occurred on national territory, the last being in the year of 2001, specifically in the Rio Grande do Sul and Acre States. These outbreaks resulted in 87 individual cases (BRAZIL, 2021).

Clinical and pathological findings

Sheep are highly susceptible to infection by the respiratory route and through skin lesions (e.g., foot lesions caused by foot-rot). The incubation period is usually 3–8 days, depending on the susceptibility of the sheep, dose of virus, and route of infection (DONALDSON & SELLERS, 2007). In sheep, the disease is generally mild. The first clinical sign observed

in a flock is lameness, which quickly affects an increasing number of sheep (HUGHES et al., 2002). Affected sheep are reluctant to walk, anorexic, and present changes in behavior, usually staying apart from other sheep. Other clinical signs include fever, vesicles in the interdigital space and mouth, and warm and painful hoof when handled. During the lambing season, the first signs in an infected flock may be the death of young lambs due to heart failure. Lambs may die before they develop vesicular lesions (KITCHING & HUGHES, 2002; DONALDSON & SELLERS, 2007).

Grossly, loss of body condition is evident in affected sheep. Early mouth lesions are characterized by erosion, most commonly prominent on the dental pad, especially where the incisors touch, but also on the gums, hard palate, lips, and tongue. Erosions are preceded by blanched areas of necrosis in the epithelium. Healing usually occurs very quickly, the sharp margination of erosion is lost after about 3 days, and the lesions progressively change into scars. Fluid-filled vesicles in the mouth are unusual and transient since the superficial epithelium is very thin and easily ruptured. Vesicles can be found in the interdigital space, on the heel bulbs, in the coronal band, and occasionally on the teats, vulva, and prepuce. In cases of affected lambs that presented heart failure, the heart is pale and soft with scattered greyish spots of variable size, mainly in the ventricles (DONALDSON & SELLERS, 2007).

Histologically, changes in the epithelium occur first in the cells of the stratum spinosum and consist of intracellular and intercellular edema, necrosis, and neutrophilic infiltration. Some lesions evolve as vesicles, resulting in the separation of the epithelium from the underlying connective tissues with the interposition of fluid. The heart lesion in lambs with heart failure is characterized by lymphohistiocytic myocarditis and, in more chronic cases, necrosis of the myocardial fibers and neutrophilic infiltration (DONALDSON & SELLERS, 2007).

Diagnosis

The diagnosis of FMD is based on the association of clinical signs and laboratory examination. For laboratory diagnosis, the sample of choice is epithelial tissue taken from animals with early FMD lesions or the liquid of the vesicles. Other samples include blood without anticoagulants for serum examination and with heparin for virus isolation, esophageal–pharyngeal samples, and milk. In a reference laboratory, the samples are tested for the presence of FMDV antigen, most performed using an indirect ELISA. Alternatively, tests for viral RNA can be performed using RT-PCR (DONALDSON & SELLERS, 2007). Sequencing of the amplification products allows determining the serotype and the origin of the strain when compared with sequence databanks.

Prevention and control

The success of the control of FMD is based on vaccine availability and adequate and fast diagnosis, quickly identifying infected animals (sick and carriers). The surveillance is an essential component, followed by quick recognition of the disease, the implementation of effective quarantine, disinfection, and flock movement controls. Even with all those measurements being strictly applied, there is no prediction of eradication of FMD within a foreseeable timeframe (KITCHING et al., 2007).

Visna-maedi

Etiology and epidemiology

Visna-maedi virus (VMV) is a non-oncogenic retrovirus of the *Lentivirus* genus, from the *Orthoretrovirinae* subfamily and *Retroviridae* family. In small ruminants, two lentiviruses are known to induce disease: VMV in sheep and caprine arthritis-encephalitis virus in goats (BLACKLAWS, 2012). Small ruminant lentivirus virions have a diameter of 80–100 nm and from the inside out comprise nucleocapsid (NC), capsid (CA), matrix (MA), and envelope (ENV), the structural genes of lentivirus are gag, pol, and parts of env (MINGUIJÓN et al., 2015). The primary tropism of the prototypical lentivirus, VMV, is for macrophages and dendritic cells (BLACKLAWS, 2012).

VMV was first isolated by Sigurdsson and collaborators in 1960, during the epidemic of slow diseases that occurred in Iceland in the 1940s after the importation of 20 Karakul rams from Germany to improve sheep production (SIGURDSSON et al., 1957; PÁLSSON, 1990). The disease resulting from this virus was named visna (wasting) and maedi (breathlessness). Transmission of VMV is primarily horizontal through inhalation of respiratory secretion; therefore, prolonged close contact between sheep, frequently associated with intensive grazing systems, is considered a significant risk factor (BLACKLAWS et al., 2004). The low seroprevalence in extensively kept sheep flocks suggested that pasture-based husbandry systems may offer conditions for the simple and inexpensive control of visna-maedi (VM) (LEGINAGOIKOA et al., 2006). In addition, milk and colostrum are efficient and important sources of infection in newborns (VAN DER MOOLEN et al., 1985).

In Brazil, lentivirus infection in small ruminants is frequently described in goats leading to

disease and economic losses. In sheep, although there are several reports of VMV seroprevalence in many regions, demonstrating very low seroprevalence of the virus in sheep flocks, only one outbreak of the clinical disease was described recently in south Brazil (CECCO et al., 2022). A moderate seroprevalence (30–60%) of VMV infection in flocks in the United Kingdom correlates with low mortality but a substantial subclinical disease (BRODIE et al., 1998). While, in countries with a high seroprevalence for VMV, like Spain, the disease is considered an important cause of economic loss due to chronic weight loss and mortality following the neurological form (BENAVIDES et al., 2006b). Investigations into the economic impact of VM are usually focused on productivity parameters, and losses are associated with reduced conception rates and a negative impact on milk production (DOHOO et al., 1987; PLOUMI et al., 2001). In Brazil, most flocks are kept in extensive grazing systems, and to this moment, there are no specific studies regarding the economic impact of VMV in sheep flocks.

Clinical and pathological findings

VM is a multisystemic disease characterized by a very long incubation period, insidious onset, and a slow progression that may affect the lung, central nervous system, mammary gland, and joints (CUTLIP et al., 1988; MINGUIJÓN et al., 2015). The clinical affection appears to depend on the tropism of the small ruminant lentivirus strain, the species affected, and the genetic background of each breed or animal (MINGUIJÓN et al., 2015).

Clinical signs develop insidiously and progress slowly and are closely related to the affected tissue. The respiratory form, maedi, is the most relevant concerning the prevalence and financial significance in sheep. Clinical signs include dyspnea, increased respiratory rate, and weight loss (CUTLIP et al., 1979). The nervous form, visna, frequently leads to stumbling, ataxia, and blindness, followed by hindlimb paralysis. Total recumbency is observed in the final stages of the disease (BENAVIDES et al., 2006b; CECCO et al., 2022). Mastitis caused by VMV is common; although, frequently subclinical, leading to important financial and epidemiological consequences since milk and colostrum can be a source of infection in newborns. Clinical signs associated with this form are difficult to detect, as the mammary gland exhibits a diffuse and non-painful hardening and tumefaction, mostly observed after delivery, which can only be confirmed by palpation (VAN DER MOOLEN et al., 1985). However, a significant decrease in milk production can be observed. The affection of joints is less frequent; however, when present, swollen carpal and, less frequently, tarsal joints are observed, leading to marked lameness (MINGUIJÓN et al., 2015). Death is inevitable once clinical signs are recognized and may occur 6 months to 1 year later. Secondary bacterial infections of the lung are commonly the cause of death (CUTLIP et al., 1988).

Grossly, the lung fails to collapse when the thoracic cavity is opened and appears large, remarkably heavy, with miliary, grey spots on the pulmonary pleural surface in a focal to a diffuse pattern (Figure 5A, 5B). A diffusely rubbery texture and occasional scattered foci of consolidation are observed. On rare occasions, gross lesions in the brain can be seen as softening of the periventricular or funicular white matter (Figure 5C) (leukomalacia) or as a granular appearance of the choroid plexus (BENAVIDES et al., 2009; VANDEVELDE et al., 2012; CECCO et al., 2022). Spinal cord lesions are rare and, at the gross examination, after transverse sectioning, consist of swollen, discolored wedge-shaped areas (BENAVIDES et al., 2006a). Gross changes in the mammary gland are often mild and consist of a firmer consistency of the gland. Arthritis is considered mild, and commonly affects the appendicular joints, and enlarged carpal joints can be observed (PÉREZ et al., 2015).

Histopathologically, in the lung, lymphofollicular hyperplasia of the bronchial-associated lymphoid tissue is the main feature (Figure 5D). Other microscopic changes include infiltration of the alveolar septa by mononuclear cells, hypertrophy of smooth muscle, and fibrosis. In areas of most severe interstitial pneumonia, which correspond to the scattered areas of consolidation, there is hyperplasia of type II pneumocytes leading to pseudo epithelialization. The mammary gland exhibits a periacinar diffuse interstitial infiltration of lymphocytes that often surround ducts, in addition to intense fibrosis, leading to profound changes in the normal acinar structure and effacing acinar epithelial cells (Figure 5E). In the neurological form, histologic changes include lymphoproliferative choroiditis and a nonsuppurative, granulomatous to necrotic leukoencephalomyelitis with secondary leukomalacia, periventricular encephalitis with mononuclear perivascular cuffs (Figure 5F), and demyelination, appearing in subependymal areas of the mesencephalon, thalamus, and medulla oblongata (BIESCAS et al., 2005; BENAVIDES et al., 2009; CECCO et al., 2022). Lymphohistiocytic perivascular cuffs and adjacent areas of macrophage infiltration of the neuroparenchyma leading to its destruction have a typical periventricular and periaqueductal distribution (funicular in the spinal cord); although they can progress to a more disseminated distribution (BENAVIDES et al., 2006b). Spinal cord lesions

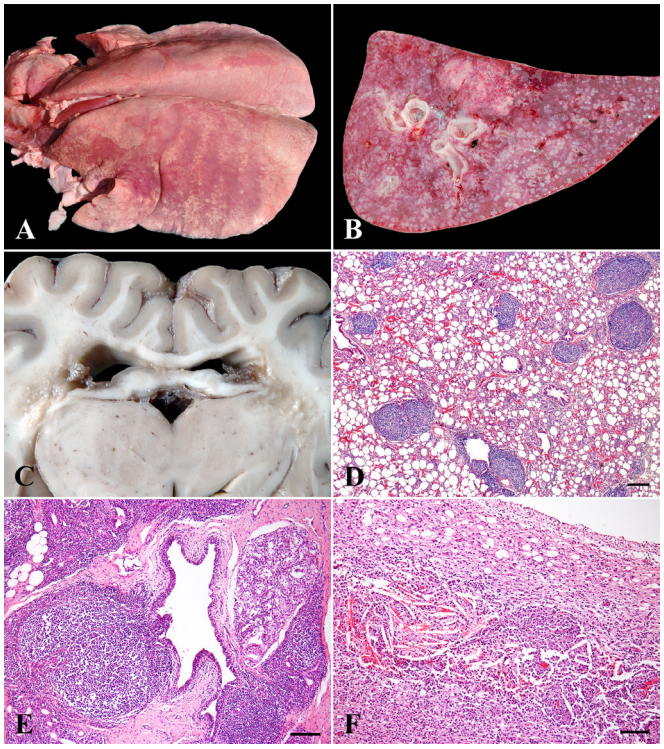

Figure 5 - Visna-maedi – A. Lungs are pale gray to pink and non-collapsed, with rib impressions and a diffusely rubbery texture. B. On the cut surface, multifocal white areas were present throughout the pulmonary parenchyma, mainly surrounding bronchi. C. In the periventricular area there is focally extensive malacia with greyish discoloration. D. Lungs with interstitial pneumonia with distinct large lymphoid follicle-like structures around bronchi, bronchioles, and vessels. H&E stain; bar = 600 µm. E. In the mammary gland, similar lymphoid follicle-like structures are evident, in addition to interstitial lymphocytic mastitis. H&E stain; bar = 200 µm. F. In the periventricular areas, moderate number of macrophages and lymphocytes infiltrate the neuropil, associated with necrotic debris, cholesterol clefts, and malacia. H&E stain; bar = 100 µm.

are similar to the ones described in the brain and are characterized by a nonsuppurative leukomyelitis, with perivascular cuffing composed of mononuclear cells, in addition to demyelination and white matter degeneration (BENAVIDES et al., 2006a). The lesions in the joints are characterized by extensive proliferation of synovial and bursal membranes, fibrosis of the joint capsule, and degeneration of articular cartilage and bone. A severe subsynovial inflammatory infiltrate composed of lymphocytes is common (PÉREZ et al., 2015).

Diagnosis

Accurate diagnosis of small ruminant lentivirus infection is of major importance for epidemiological research and control programs since VMV can be widely spread within the flock before clinical cases can be observed (MINGUIJON et al., 2015). VMV infection is efficiently detected by serological methods, including agar gel immunodiffusion assay (AGID) and ELISA, and molecular techniques (PCR) (DE ANDRÉS et al., 2005). Peripheral blood and refrigerated tissue from organs (lung, CNS, mammary gland, and joints) can be used to perform molecular PCR-based techniques (DE ANDRÉS et al., 2005; 2013). The use of milk samples in PCR has given variable results, while in semen samples, PCR sensitivity can be decreased by intermittent shedding of infected cells and the presence of PCR inhibitors (PAULA et al., 2009).

The target sequences for molecular tests include all the genome (LTR, gag, pol, and env genes). The LTR and pol regions are more conserved, while env has the highest variability. Primer sequences chosen from a conserved region are better for the development of a PCR assay and also to prevent false-negative results (DE ANDRÉS et al., 2005).

Prevention and control

Due to the long course of VMV infection, control methods may take several years to be implemented successfully. VM control for an infected flock can either be via eradication or by conservative management (MINGUIJÓN et al., 2015). Therefore, for VMV eradication, several strategies can be applied including depopulation and repopulation with MV-free sheep, selective culling of infected animals and their progeny, and artificial rearing of lambs. In cases were more conservative management is desired the flock must be frequently tested and be separated in two groups according to their infection status (LEGINAGOIKOA et al., 2006). The seronegative group must be kept isolated from the seropositive group and strict hygiene must be performed. Also, the reduction of stocking density (sufficient area and volume) and adequate ventilation are important to minimize horizontal transmission (BLACKLAWS et al., 2004).

Enzootic nasal tumor

Etiology and epidemiology

Enzootic nasal tumor (ENT) is a contagious viral disease of sheep and goats characterized by neoplastic growth of the ethmoid mucosa in the nasal cavity. The condition is caused by the enzootic nasal tumor virus (ENTV), which is a member of the family *Retroviridae*, and genus *Betaretrovirus* (DE LAS HERAS et al., 2019). This retrovirus is closely related to Jaagsiekte sheep retrovirus, which causes the ovine pulmonary adenocarcinoma (COUSENS et al., 1999), and the enzootic nasal tumor virus of goats (ORTÍN et al., 2003).

ENT occurs in many countries all over the world, except for Australia, New Zealand, and Great Britain. The first case of the disease was described in Germany (COHRS, 1953). In Brazil, the first publication associating a nasal tumor to ENTV in sheep was made in 2019, specifically in the Rio Grande do Sul state (CECCO et al., 2019). Epidemiological data indicate that ENTV prevalence in the affected flock is variable ranging from 0.1 to 15% and preferentially affects young adults (3–5 years) (DE LAS HERAS et al., 1998). No genetic, sex, or breed predisposition has been determined (DE LAS HERAS et al., 2019).

Clinical and pathological findings

Clinically, the disease is characterized by inspiratory dyspnea with stertorous breathing, sneezing, head shaking, dyspnea, facial asymmetry with deformation of the skull bones (mainly frontal and maxillary), and seromucoid nasal discharge, exophthalmos, and fistula. The breathing difficulty induces anorexia and gradual weight loss (Figure 6A). The severity of clinical signs is directly associated with the size of the mass obstructing the nasal cavity (DE LAS HERAS et al., 1991; 2019).

The tumors originate unilaterally or bilaterally in the olfactory mucosa of the ethmoid or nasal turbinates and consist of a lobular mass, soft, pinkish-white, that is locally invasive and can completely obstruct the nasal cavities (Figure 6B), but rarely metastasize. The erosion of maxillary, cribriform plate, and other skull bones and tumor invasion of the orbit, compressing retro-ocular structures and leading to exophthalmos, are frequently observed in severe cases (DE LAS HERAS et al., 1991; 2019). Clear mucus exudate, nasal polyps, soft yellow areas consistent with necrosis, and distortion of turbinates and of the medial septum can be associated with the neoplastic mass. Additionally, secondary bacterial infections have been reported inducing septicemia and pneumonia (DE LAS HERAS et al., 2003b).

Microscopically, the tumor consists of proliferating secretory, non-ciliated cells with an acinar, papillary, tubular, or cystic arrangement, interspersed with variable amounts of the fibrovascular stroma (Figure 6C). The low degree of anisokaryosis, low mitotic rate, and apparent absence of metastases (local lymph nodes and other organs) define the tumor as a 'low-grade adenocarcinoma' (Figure 6D). In larger tumors, necrosis is common and can be associated with severe inflammatory infiltrate and hemorrhage. Tumor cells express the envelope protein of the virus, which can be detected by immunohistochemistry (WALSH et al., 2013) and retrovirus-like particles can be observed in the tumors by electron microscopy (DE LAS HERAS et al., 2003b).

Diagnosis

The diagnosis of ENT is based on pathological features and viral identification. The ENTV-1 genome has been completely sequenced, including viral proteins as *gag*, *pro*, *pol* and *env* (COUSENS et al., 1999). The sequencing is useful to distinguish ENTV and JSRV since they have an amino acid similarity greater than 95%. The differences between them occur at the 3′ end of *env* and in the U3 LTR region; and the region of the open reading frame (ORFX) described for JSRV

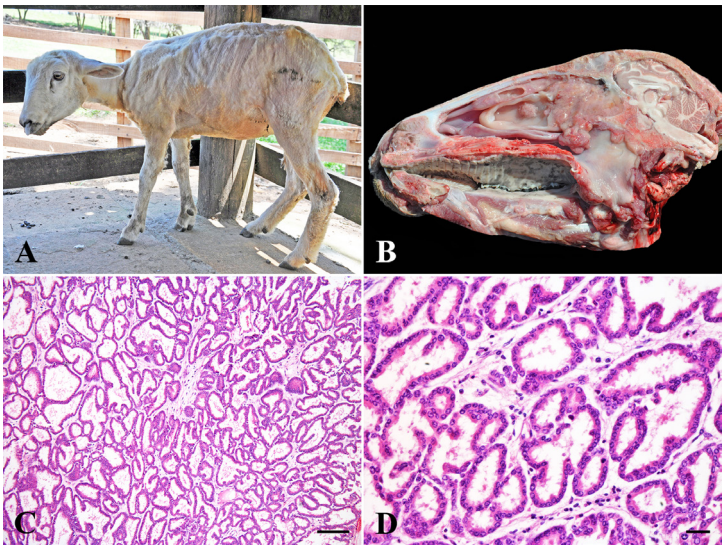

Figure 6 - Enzootic nasal tumor – A. Ewe shows emaciation, white mucopurulent nasal discharge, and mild facial enlargement in the nasal bone region. B. Tumor is characterized as a firm and white mass, which completely occluded the right nasal cavity. C. Neoplastic proliferation was characterized by epithelial cells, interspersed with scarce fibrovascular stroma. H&E stain; bar = 500 µm. D. Neoplastic epithelial cells arranged in a papillary growth pattern with mild anisocytosis and moderate anisokaryosis. H&E stain; bar = 45 µm.

contains two stop codons in ENTV (COUSENS et al., 1999). Several specific PCR protocols are available to detect the viral genome in tissues. Studies concluded that ENTV-1 is usually confined to the tumor and is rarely found in other tissues. Therefore, samples such as blood would not be suitable for the detection of ENTV-1 on infected animals. Identification of infected animals without clinical manifestation is difficult. Samples of the nasal tumor are considered to be the specific material to be sent to virology for viral identification (DE LAS HERAS et al., 2019).

Prevention and control

Flock control of enzootic tumors is difficult due to the fact that there is no serologic test to identify animals with preclinical disease. Since enzootic nasal tumors can be spread by nasal discharge, infected animals should be isolated and culled as soon as diagnosed (DEMARTINI & YORK, 1997).

Ovine pulmonary adenocarcinoma

Etiology and epidemiology

Ovine pulmonary Adenocarcinoma (OPA), also known as Jaagsiekte, is a transmissible lung tumor caused by Jaagsiekte sheep retrovirus (JSRV). This virus is responsible for inducing the oncogenic transformation of alveolar and bronchiolar secretory glands, leading to severe pulmonary edema (DE LAS HERAS et al., 2003a; GRIFFITHS et al. 2010). Several studies determined that natural transmission of JSRV occurs most commonly via the aerosol route, and sheep that produce lung fluid are likely to be the most effective in spreading the disease (COUSENS et al., 2008; GRIFFITHS et al., 2010). Infection of the lambs may occur by the ingestion of milk or colostrum (GRECO et al., 2008).

OPA was firstly described in South Africa in the 19th century and, since then, has been identified in many countries, with the exceptions of New Zealand, Australia, and Falkland Islands (GRIFFITHS et al., 2010). In South Africa, Scotland, and South America, 5-20% of the infected sheep contain pulmonary tumors (CASWELL & WILLIAMS, 2016). In Brazil, the only case described occurred in the late 90' in a Karakul sheep in RS state (Figure 1), offspring of animals imported from Germany (DRIEMEIER et al., 1998). Since then, no other case of OPA has been registered in the Brazilian territory. The highest mortality rates from OPA are reported in the first years after the introduction of JSRV, and as the disease

becomes endemic, the mortality rate falls to around 1–5% (SHARP & DEMARTINI, 2003).

Clinical and pathological findings

OPA has been recorded in sheep ranging in age from 2 months to 11 years, although clinical cases are frequently recorded in sheep of 2 to 4 years old (HUNTER & MUNRO, 1983). In typical cases, infection by JSRV is clinically silent until the tumor is sufficiently advanced to compromise respiration or cause the animal to lose its condition. The incubation period may last from months to years (SHARP & DEMARTINI, 2003). The first indicator of OPA in a sheep flock is an increased number of deaths in adult sheep from pneumonia that does not respond to antibiotic treatment (GRIFFITHS et al., 2010). Common clinical signs include dyspnea, which can be accentuated by exercise, weight loss despite normal appetite, coughing, and the production of abundant amounts of frothy, clear, or milky fluid in the lung, that drains from the nostril when the sheep lowers its head. An easily performed test in suspected sheep is called the "wheelbarrow test," which consists of lifting the rear end to observe the fluid (GRIFFITHS et al., 2010). The fluid production can vary from 40 to 400 ml per day (COUSENS et al., 2009). After presenting clinical signs, sheep usually die a few days later and can die abruptly after exercise or exposure to cold (GRIFFITHS et al., 2010).

During the postmortem examination of naturally infected sheep with classical OPA, a large amount of frothy fluid is observed exuding from the nasal cavity. Similar fluid is noticed filling the tracheal lumen. In advanced stages of the disease, it is common to report sheep in regular to poor body condition. At the opening of the thoracic cavity, the lung fails to collapse, and is heavy and filled with fluid. Multifocally, whitish to greyish, raised nodules that can occupy large portions of the cranial lung lobes are observed. At the cut surface, the nodules are solid, with a grey discoloration, granular surface, and exude frothy fluid. In addition, firm foci of fibrosis or areas of necrosis and abscessation are frequently reported (GRIFFITHS et al., 2010). Pleurisy, often with a chronic fibrous appearance, is a common finding in the affected lung (DE LAS HERAS et al., 2003a). As with atypical OPA, grossly, the neoplasm tends to be more nodular in both early and advanced tumors instead of diffuse (DE LAS HERAS et al., 2003a). The nodules may be solitary or multiple, commonly found in the diaphragmatic lobes. They are pearly white in color, dry, and have a hard consistency (DE LAS HERAS et al., 2003a). Regional lymph nodes (bronchial and mediastinal) can present edema and are considered the most common site of metastasis (DEMARTINI et al., 1988; ROSADIO et al., 1988). Other organs such as the liver, kidney, skeletal muscle, and heart can have metastasis but are considered rare (MACKAY & NISBET, 1966; NOBEL et al., 1969; HUNTER & MUNRO, 1983).

Histologically, a neoplastic epithelial proliferation originates from the alveolar and bronchiolar epithelium, specifically type II pneumocytes, the secretory epithelial cells in the lung. The neoplastic cells are arranged in multifocal acinar and papillary patterns that expand into adjacent parenchyma (Figure 7A). These are supported by fibrovascular connective tissue and frequently compress the neighboring alveoli causing atelectasis. Cuboidal or columnar neoplastic cells replace the normal flat type I pneumocytes, but the structure of the alveolar wall is generally maintained (Figure 7B). The cytoplasm can be homogeneously eosinophilic or vacuolated, and nuclei are uniform and rounded. Mitotic count is usually low. In areas of increased malignancy, solid masses of pleomorphic cells with a high mitotic rate and scattered foci of necrosis are found. Characteristically, the alveoli adjacent to the neoplastic nodules are filled with enlarged, foamy macrophages, which are called para-adenomatous areas. The main histological difference between classical and atypical OPA is that in the latter, the macrophages are much less abundant, while infiltration of the tumor stroma by inflammatory cells and connective tissue is prominent (GARCÍA-GOTI et al., 2000; DE LAS HERAS et al., 2003a). JSRV virions can be visualized in OPA-affected lungs through electronic microscopy (DE LAS HERAS et al., 2003a).

Diagnosis

PCR on blood samples can be employed to detect JSRV-infected cells; however, the proportion of infected cells in blood is very low, and such tests may fail to identify infected animals (LEWIS et al., 2009). The most successful method for identifying early OPA has been PCR testing of bronchoalveolar lavage samples collected from live animals (VOIGT et al., 2007). From deceased sheep, lung tissue samples can be collected and refrigerated for posterior submission to PCR testing (DE LAS HERAS et al., 2003a).

Prevention and control

Currently, there are no established vaccines or treatments for OPA and death inevitably occurs in clinically affected animals. Therefore, prevention methods must be implemented in regions where the condition is common. The methods include

quarantining, cleaning, and disinfection of contaminated areas and equipment, artificial rearing of lambs, and removal of affected animals and their offspring as soon as the disease is detected (DEMARTINI et al., 1988; VOIGT et al., 2007).

Border disease

Etiology and pidemiology

Border disease virus (BDV) of sheep is from the family *Flaviviridae*, genus *Pestivirus*, is genetically and antigenically closely related to bovine viral diarrhea virus (BVDV) and classical swine fever virus (CSFV). Cross-infection between species can occur, and viruses are now grouped by their antigenic reactivity and their nucleotide sequences at selected genomic regions (NETTLETON & WILLOUGHBY 2008). The genus is characterized by enveloped, spherical particles with approximately 50 nm in diameter, and its genome is a positive single-stranded RNA molecule (NETTLETON et al., 1998). The genome contains a single open reading frame (ORF) and encodes 4 structural proteins, the capsid (C) and three envelope glycoproteins (Erns, E1, and E2), and 7 to 8 non-structural proteins (Npro, p7, NS2–3, NS4A, NS4B, NS5A, and NS5B), which are flanked by 5′ and 3′ large untranslated regions (UTRs) (MEYERS & THIEL, 1996; BECHER et al., 2012).

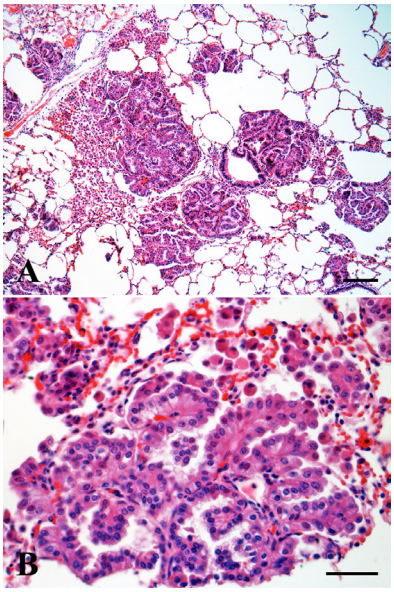

Figure 7 - Ovine pulmonary adenocarcinoma – A. Histopathology of the lesions reveals a multifocal characteristic growth of cuboidal cells along the alveolar walls and in the bronchi. H&E stain; bar = 200 µm. B. The tumor is a mixed adenocarcinoma with acinar and papillary growth patterns. H&E stain; bar = 50 µm.

In sheep, this virus is associated with congenital disease and is manifested by barren ewes, abortion, and stillbirths, also the birth of small, weak lambs that can present tremor, abnormal body conformation, and hairy fleeces that are called Hairy Shakers (NETTLETON & WILLOUGHBY, 2008; CONSTABLE et al., 2017).

Border disease (BD) was first detected in 1959 in the border region of England and Wales and is now considered widespread in Europe, Australia, Asia, and North America. BD has also been reported in Israel and North Africa (NETTLETON et al., 1998). In Brazil, a neurological disorder in sheep associated with BDV was described in 1998 (PESCADOR et al., 2004). However, another study could not detect any positive sample using RT-PCR in 2,672 small ruminant serum samples from Northeast Brazil (SILVEIRA et al., 2018). The spread of BDV within a flock may take years in sheep reared on grass but is highly favored by intensive systems of management, which allow close contact among animals (NETTLETON et al., 1998; NETTLETON & WILLOUGHBY, 2008).

Clinical and pathological findings

Healthy newborn and adult sheep exposed to BDV will experience only mild or subclinical disease. Slight fever and mild leukopenia are associated with a short-lived viremia detectable between days 4 and 11 post-infection, after which serum neutralizing antibody appears (NETTLETON et al., 1998). The main clinical signs of BDV are seen following the infection of pregnant ewes. Fetal death can occur at any stage of pregnancy, although it is more common at early gestation (NETTLETON et al., 1998). Clinically, affected lambs have a low chance of survival. Many die early in life, while survivors have a poor growth rate and an increased susceptibility to other diseases. Less severely affected lambs and apparently normal persistently infected lambs can survive for years and are considered the most important source of infection (NETTLETON et al., 1998; NETTLETON & WILLOUGHBY, 2008).

Affected lambs may have low birth weight, abnormalities of conformation and fleece, muscular tremors, hypermetria, general incoordination, ataxia, and occasionally enteric dysfunction (PESCADOR et al., 2004; CONSTABLE et al., 2017). The neurological signs can gradually decline and disappear

by 3 to 6 months of age; however, weakness, swaying of the hindquarters, and fine trembling of the head may reappear at times of stress (NETTLETON et al., 1998; NETTLETON & WILLOUGHBY, 2008).

Gross findings frequently include abnormal wool coat, reduction in the size of the brain, especially cerebellum (cerebellar dysplasia), bilateral dilatation of the lateral ventricles (hydranencephaly), porencephaly, and arthrogryposis (PESCADOR et al., 2004). Histologically, areas of cellular disorganization in the cerebellar cortex, reduction of the granular layer of the cerebellum associated with decreased cell density, and presence of large cytoplasmic vacuoles in the molecular layer are observed (Figure 8) (PESCADOR et al., 2004). In addition, hypomyelinogenesis, nodular periarteritis, necrosis, and inflammation of the germinal layers of the central nervous system have been described (THOMSON & HARKNESS, 1994; CONSTABLE et al., 2017). The fleece abnormalities of BD-affected lambs result from the increased size of primary wool follicles and decreased numbers of secondary wool follicles in the skin (NETTLETON & WILLOUGHBY, 2008). Defects of vision are probably of central origin rather than the result of focal retinal dysplasia (CANTILE & YOUSSEF, 2016).

Diagnosis

Several diagnostic methods for pestiviruses have been reported (NETTLETON & ENTRICAN, 1995; NETTLETON et al., 1998). To detect the antibody-negative, virus-positive, and persistently infected sheep, all animals in a suspected group should be blood-sampled. From live lambs, a heparinized blood sample can be used for virus isolation in cell culture. When tissues are available, the best is to submit fresh samples of the thyroid, kidney, brain, spleen, gastrointestinal tract, and lymph nodes for antigen detection. Serological examination of individual sheep for BDV antibodies is rarely helpful, but antibody testing of a 10 percent sample of different age groups of animals can be useful for demonstrating the presence and extent of BDV infection in a flock (NETTLETON & WILLOUGHBY, 2008). RT-PCR assay may be used for the diagnosis of persistently infected animals or fetuses (VILČEK & PATON, 2000). Immunohistochemical analysis using monoclonal anti-BVDV antibodies may be used to detect pestiviruses in affected ovine fetuses and lambs (THÜR et al., 1997; CONSTABLE et al., 2017).

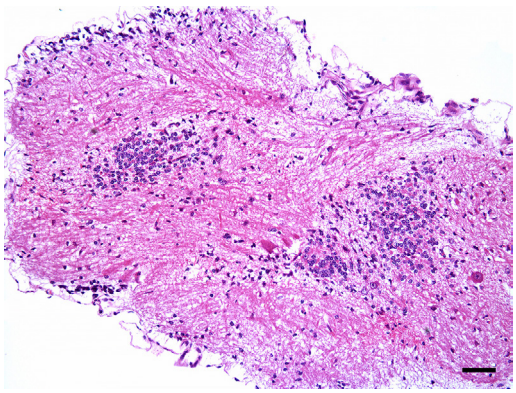

Figure 8 - Border disease – Cellular disorganization in the cerebellar cortex, reduction of the granular layer of cerebellum associated with decreased cell density, and presence of large cytoplasmic vacuoles in the molecular layer. H&E stain; bar = 100 µm.

Prevention and control

For the appropriate control of BDV in a sheep flock, two essential requirements must be followed: all PI sheep must be identified and the measures to prevent infection of susceptible pregnant ewes, especially during the first half of gestation must be established. Because of the risk of infection of sheep from PI cattle it is essential that pregnant ewes are never mixed with cattle (NETTLETON et al., 1998).

Other common strategies to minimize disease exposure are recommended including testing animals before the purchase and quarantining new animals before introducing them to the flock. Ideally, replacement females should be home-bred, and all purchased rams should be blood-tested to ensure they are not persistently infected. Where females are also purchased, the feasibility of bloodtesting them should be considered. Recently purchased females should always be mated and keptseparate from the rest of the flock until lambing time (NETTLETON & ENTRICAN, 1995; NETTLETON et al., 1998).

There are only a few commercial vaccines for the control of BDV, and it is not licensed in all countries. Further vaccine development is required, with candidate vaccines being tested for efficacy in pregnant sheep (VOGEL et al., 2001; NETTLETON & WILLOUGHBY, 2008).

CONCLUSION

Viral infectious agents responsible for causing illness in sheep are associated with moderate to severe economic losses resulting from a decrease in milk and meat production, deaths, and cost of treatment.

Brazil is one of the largest sheep producers in the world, therefore, highly dependent on the health status of the flock. In order to obtain and maintain good health status, veterinarians must be able to diagnose and implement treatment and control measures. This article was also designed to be a practical reference for field veterinarians and sheep owners, in order to assemble data regarding the main viral diseases in sheep in the Brazilian territory to be used as a tool for the formulation of prevention and control measures for the national flock. Most of the viruses described in this paper are transmitted via close contact between sheep, and via the oropharyngeal route by virus shed in secretions of saliva, nasal mucus, and aerosol. Therefore, similar prevention and control measures apply to many of the conditions described in this paper. Testing animals before introducing them to a flock or performing quarantine for purchased animals can prevent the introduction of viral agents such as contagious ecthyma virus, lentivirus (VMV), ENTV, ovine pulmonary adenocarcinoma virus, BDV, and BTV.

This manuscript highlights the importance of the recognition and appropriate diagnosis of these viral diseases, providing a complete pathological description, recent national data regarding diseases status obtained from official sources, and which diagnostic tools can be performed to provide a conclusive diagnosis. The data assembled in our paper was also organized with the intention of being a quick consultation guide for veterinarians.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

AUTHOR'S CONTRIBUTIONS

BSC, IRS, FAM, and SPP were responsible for study conception, and writing-original draft preparation. LS, DD, CSLB, and CWC were responsible for reviewing the manuscript.

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