Diagnostic Exercise
From The Davis-Thompson Foundation*

Case #:**212** Month: **May**; Year:**2023**
Answer Sheet

Title: *Non-suppurative and necrotizing leukoencephalitis and interstitial pneumonia (Maedi-visna) in sheep*

Contributors: Fernanda F. Perosa, DVM, Jean C. O. Menegatt, DVM, Manoela M. Piva, DVM, MSc, Vitor W. Horn, DVM, Teane M. A. Gomes, DVM, MSc, PhD, Ricardo E. Mendes, DVM, MSc, PhD. Laboratório de Patologia Veterinária, Instituto Federal Catarinense *Campus* Concórdia (IFC-Concórdia), Concórdia, SC, Brazil. Corresponding author: fernandaperosa7@gmail.com

Clinical History: Within two months, three adult sheep fell ill in a 40-sheep flock (flock 1). Sheep 1 was a 3-year-old Texel ewe who developed neurological signs of ataxia, lethargy, recumbence, and difficulty in staying, dying one week after the onset of the clinical signs. Sheep 2 was a 2-year-old Texel ewe, and Sheep 3 was a 2-year-old Texel ram which both presented with anorexia, loss of body weight, and marked dyspnea for three weeks. The sheep were treated with antibiotics and antiparasitic drugs, however, they showed no health improvement and were later euthanized. In another sheep flock (flock 2) from the same municipality, for four months, it was reported that many sheep presented respiratory signs mainly characterized by marked dyspnea. Two Texel ewes from this herd, a 9-year-old (Sheep 4) and a 2-year-old (Sheep 5), were submitted for necropsy.

Gross Findings: The five sheep were in poor body condition. On the surface of the central nervous system of Sheep 1, blood vessels were moderately and diffusely engorged. In transverse sections of the brain, the white matter, just above of the caudate nucleus (Fig. 1), has a 1.5 cm in diameter focal area of softening. In Sheep 2-5, the lungs were pale to gray, rubbery, non-crepitant, markedly and diffusely noncollapsed, and heavy (Fig. 2). Dark millimetric areas associated with white and slightly elevated nodules, up to 3 mm in diameter, were also seen at the pleural and cut surfaces of the lungs (Fig. 3). Additionally, Sheep 4 presented significant and diffuse consolidation of the cranioventral lung lobes (Fig. 2).

Gross and Histological Images:

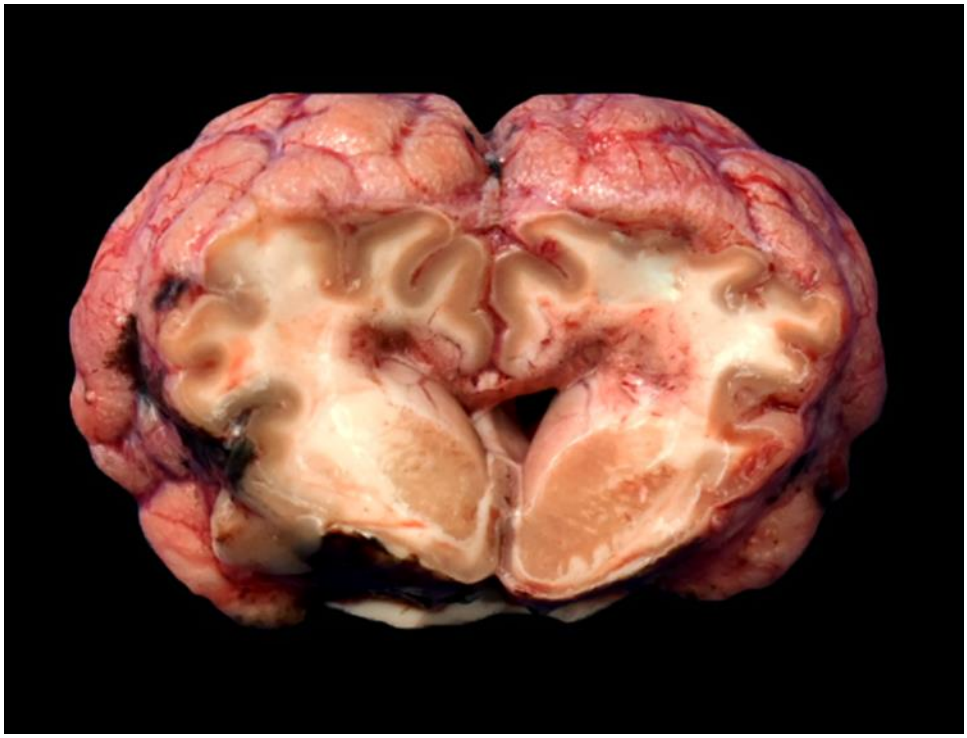

Figure 1. A transverse section of the brain, at the periventricular region, reveals a focal and irregular area of softening measuring 1.5 cm, which is in the white matter just above the caudate nucleus.

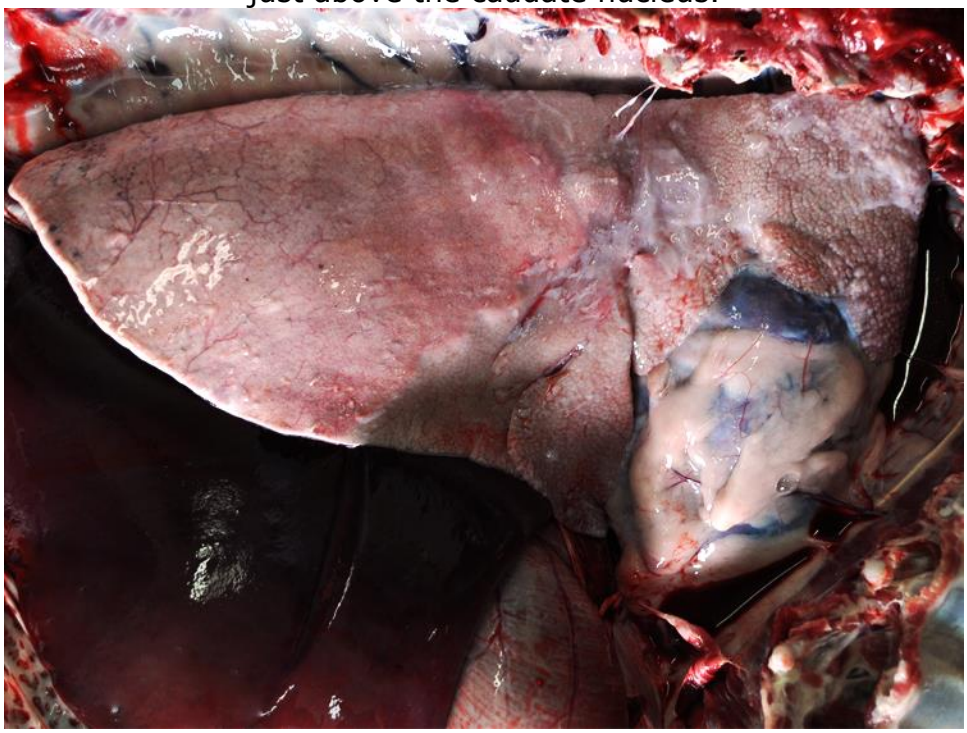

Figure 2. The caudal lobes are pale to gray and markedly and diffusely noncollapsed with slight interlobular edema. Irregular and opaque pleural surface with occasional dark millimeters areas. Marked and diffuse consolidation of the cranioventral lung lobes.

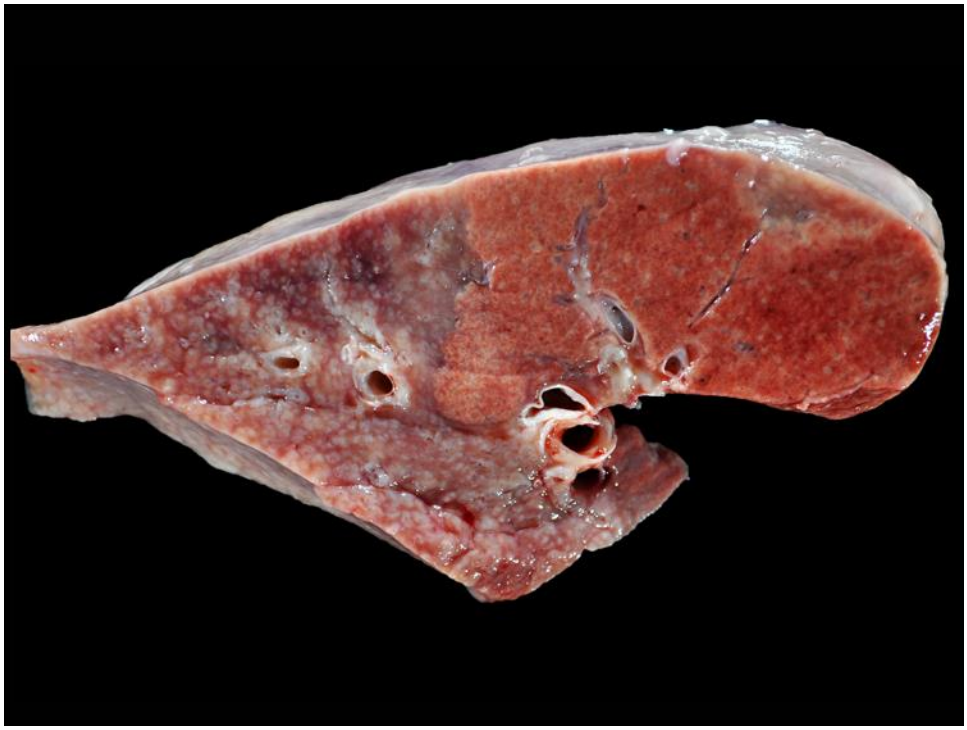

Figure 3. Cut surface of the lung presenting multifocal to coalescing and elevated white nodules measuring up to 3 mm in diameter.

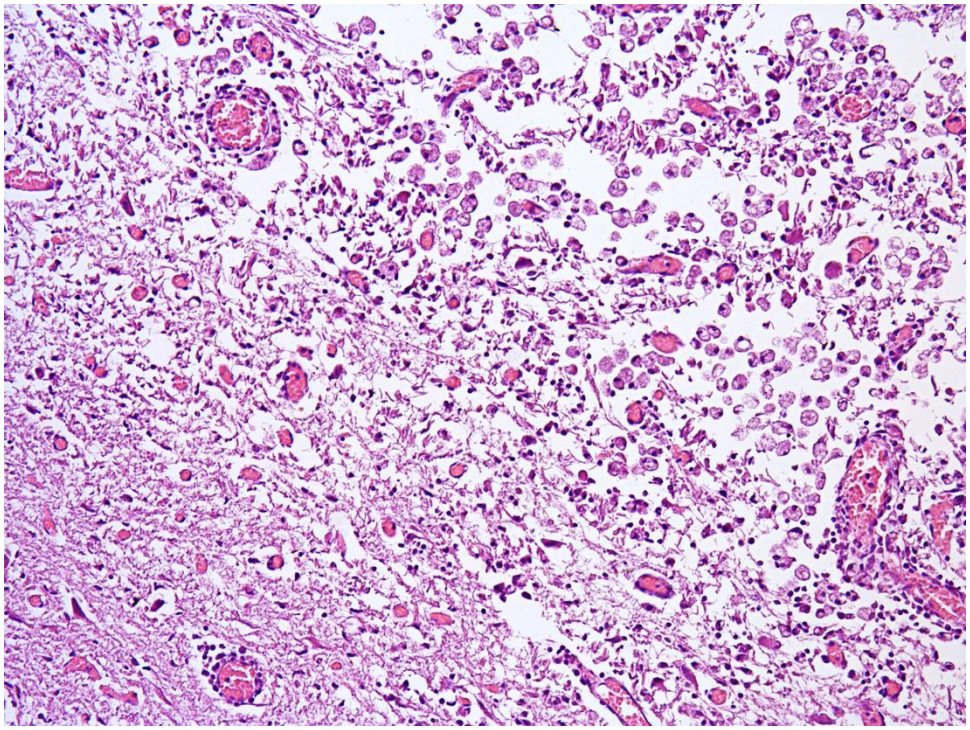

Figure 4. Focally extent area of marked neuropil rarefaction, cellular debris, marked infiltration of gitter cells (malacia) and perivascular cuffings consisting of lymphocytes and plasm cells.

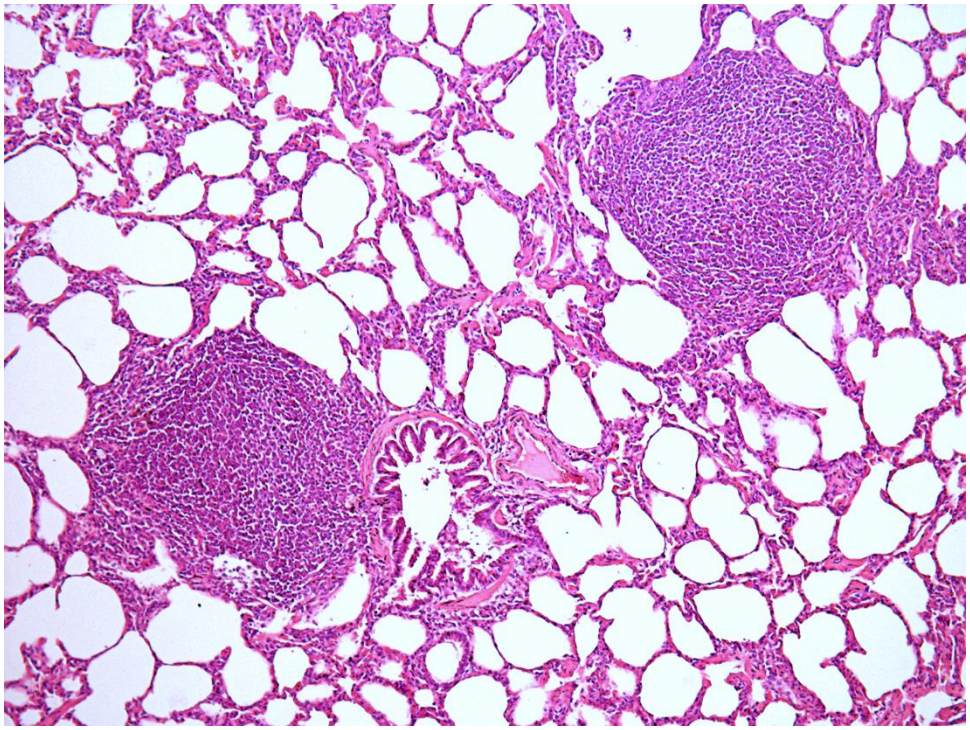

Figure 5. Marked and multifocal hyperplasia of the bronchial lymphoid associated tissue (BALT).

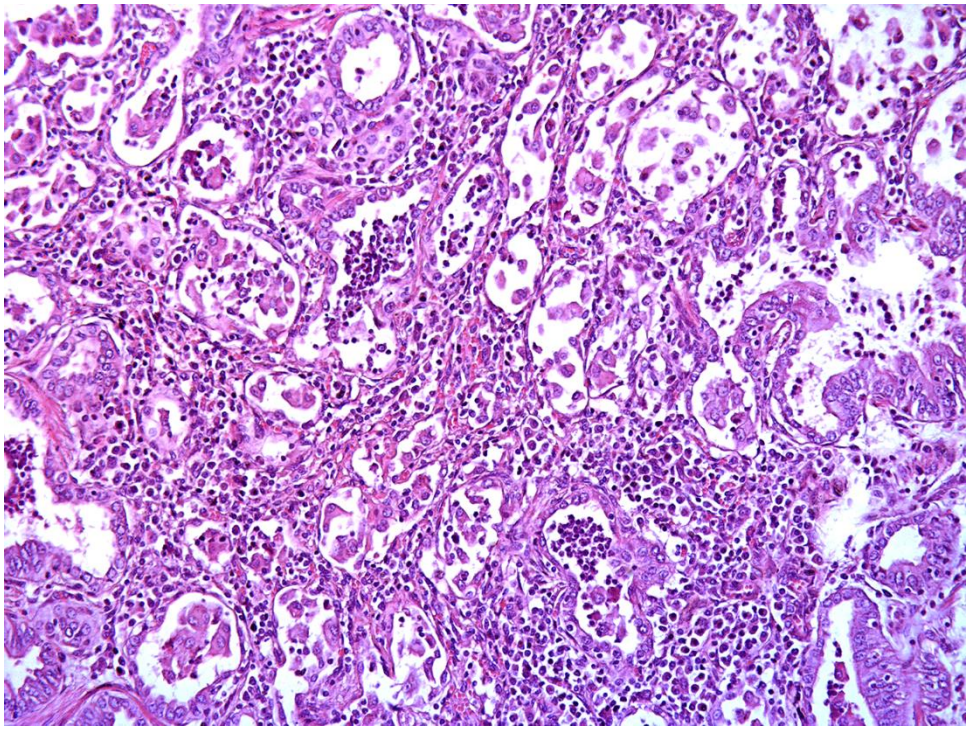

Figure 6. Marked alveolar epithelialization (proliferation of type II pneumocytes) interstitial infiltration of lymphocytes, plasm cells and histiocytes, accumulation of neutrophils inside alveolar spaces, and mild multifocal hyperplasia of bronchial and bronchiolar smooth muscles.

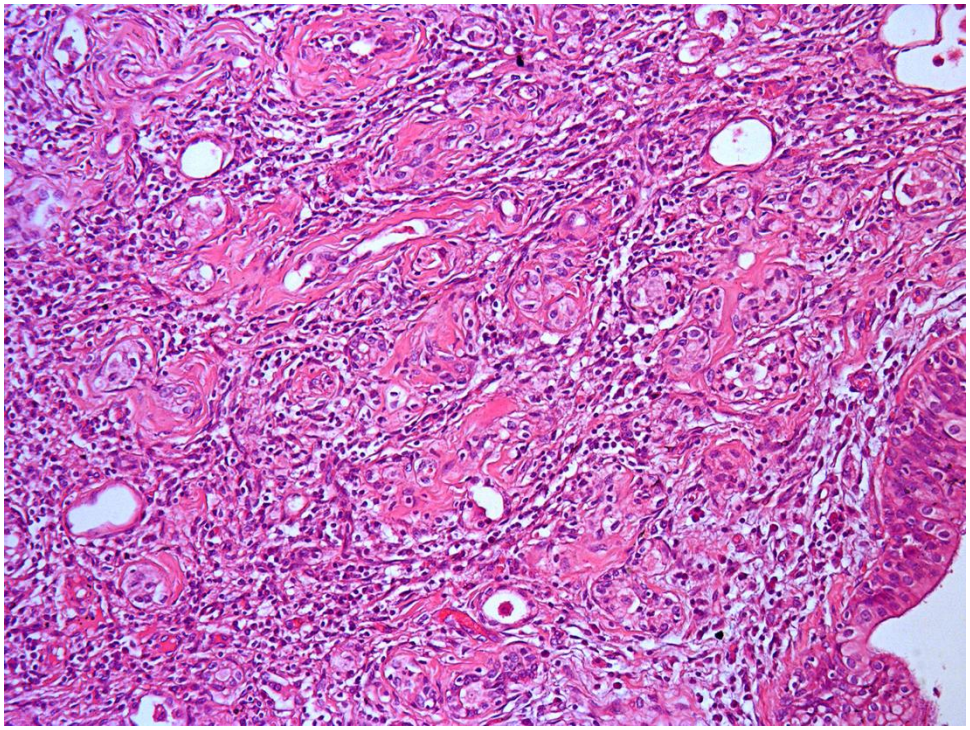

Figure 7. Marked and diffuse interstitial proliferation of fibrous connective tissue and hyperplasia of bronchial epithelium.

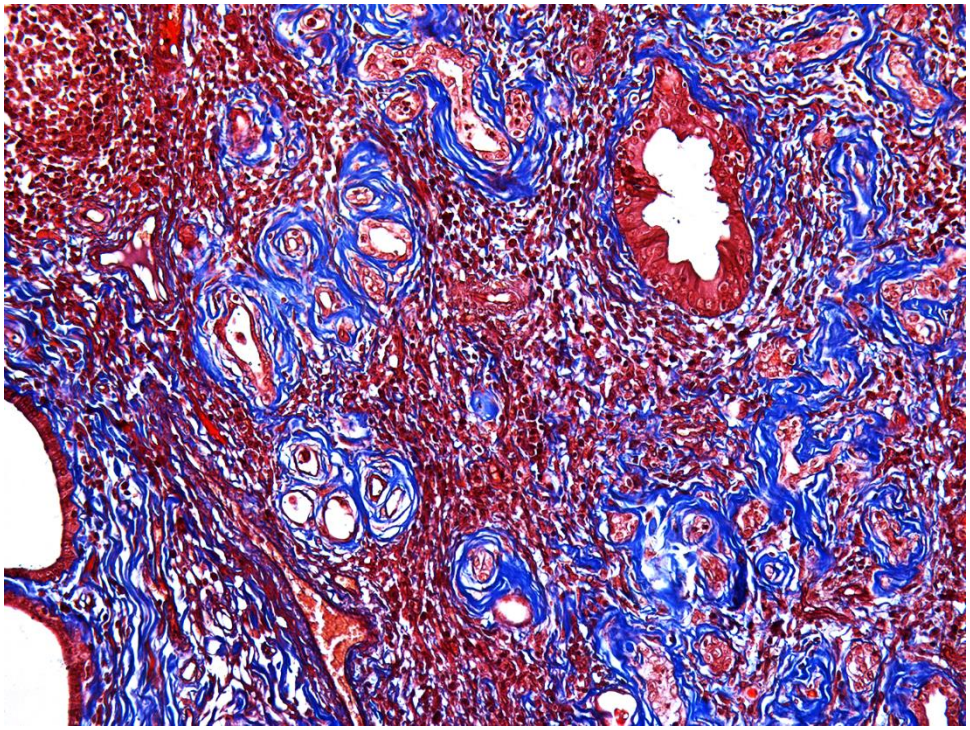

Figure 8. Marked and diffuse proliferation of fibrous connective tissue in the pulmonary interstitium enhanced by Masson's Trichrome.

Histological Description: Brain (Sheep 1): the white matter in the proximity to the ventricles, has areas of rarefaction associated to marked infiltration of gitter cells (malacia), lymphocytes and plasm cells. Perivascular cuffings consist of lymphocytes and plasm cells and swallowing of endothelial cells (Fig. 4). Sheep 1 also presented moderate and multifocal hyperplasia of bronchial associated lymphoid tissue (BALT), and mild multifocal perivascular infiltration of lymphocytes in the epicardium, liver and kidneys. Lung (Sheep 4): interstitial inflammatory infiltration of lymphocytes and macrophages, moderate and multifocal BALT hyperplasia (Fig. 5), ectasia of peribronchiolar glands and moderate bronchiectasis. Alveolar epithelization, proliferation of type II pneumocytes and multifocal areas of alveolar edema. Hyperplasia of bronchial and bronchiolar smooth muscles. Mainly in the cranioventral lobes, accumulation of eosinophilic material and degenerated neutrophils inside bronchi and bronchiole (Fig. 6). Marked and multifocal interstitial proliferation of fibrous connective tissue (Fig. 7 and 8.). The lungs o Sheep 2 and 3 had proliferation of syncytial cells. Sheep 2 also presented moderate and multifocal interstitial inflammatory infiltration of lymphocytes and plasm cells in the mammary gland.

Morphological diagnoses:
1.Brain, chronic multifocal, marked non-suppurative and necrotizing leukoencephalitis.
2. Lungs: chronic diffuse, marked proliferative interstitial pneumonia.

Etiology: Maedi-visna virus (*Lentivirus*)

Name of condition: Maedi-visna

Comments: Visna-Maedi virus (VMV) and caprine arthritis encephalitis virus (CAEV) of goats and sheep belong to the genus Lentivirus, family Retroviridae, and are commonly referred to as small ruminant lentivirus (SRLV). CAEV causes caprine arthritis-encephalitis in goats, and VMV causes visna-maedi disease in sheep (6). Transmission of these two SRLVs can occur between sheep and goats (2). In both, four manifestations are possible: mastitis, arthritis, interstitial pneumonia (maedi, or ovine progressive pneumonia), and encephalomyelitis (sheep visna).

MVV was first reported in Iceland, when the virus was introduced in 1933 by imported sheep from a German farm. The imported sheep were kept in quarantine for two months before being distributed to some farms in Iceland. However, these animals were carriers of the MVV, to which Icelandic sheep were extremely susceptible (5). Later, other sheep from Iceland started to develop the previously unknown central nervous system disease and invariably fatal interstitial pneumonia in 1935 and 1939, respectively. In 1957, MVV was isolated in tissue cultures of brain and lungs of sheep from Iceland (5, 9).

Newborn lambs get infected through the consumption of colostrum and milk from infected ewes. Respiratory secretions can lead to horizontal transmission of the virus within the herd (2). The disease develops slowly, and the incubation period usually exceeds two years (3).

MVV infection in sheep causes chronic pneumonia, encephalitis, arthritis, and mastitis, with these syndromes occurring either independently or concurrently. The respiratory form "maedi" ("dyspnea" in Icelandic) in sheep is the main presentation, manifesting with progressive dyspnea, hyperpnoea, abdominal breathing, and weigh loss in adult sheep (3). Encephalitis, known as "visna" ("fading away" in Icelandic) is way less common than the respiratory form, and results in ataxia, trembling, paresis, paralysis and profound weight loss (3). Mastitis and arthritis are rare forms of the disease and present with agalactia and hardness of the udder, or lameness and swollen joints, respectively (3).

Sheep with MV have the lungs remarkably heavy, pale, gray or tan, with a rubbery texture, and failing to collapse when the thorax is opened at the necropsy. These lesions are diffuse but most prominent in the caudal lobes and multiple coalescing gray and firm foci are usually seen, along with mediastinal and bronchial lymph nodes presenting lymphadenopathy. Secondary bacterial bronchopneumonia and coinfection with lungworms are common in sheep with MV. At microscopic examination, there is interstitial pneumonia, characterized by infiltration of lymphocytes, plasm cells, and macrophages thickening the alveolar septa and forming cuffs around the blood vessels and airways. Commonly, these inflammatory infiltrates form lymphoid nodules, near bronchi and bronchioles (BALT hyperplasia). Additionally, hypertrophy of smooth muscle and interstitial fibrosis may happen, contributing to the thickening of the alveolar septa (3).

In sheep with the neurological presentation of MV, lesions are mainly found periventricular in the brain and affecting the white matter of the spinal cord (3). In a study with 64 sheep with meningoencephalomielitis caused by natural infection with MVV, lesions were predominantly found in the cerebellar peduncles, followed by the corpus callosum, hippocampus, and thoracic spinal cord (1). Histologically, the lesions consist of a non-suppurative meningoencephalomielitis with infiltration of lymphocytes and/or histiocytes, along with gliosis, malacia, and, sometimes, mononuclear infiltrates forming lymphoid follicles in choroid plexus (1, 3). At immunohistochemistry, it may show immunolabelling of the MVV in macrophages from the areas with malacia, at the periphery of the damaged areas (1).

In a study conducted in the sheep flocks reported here, 45% of the animals were positive to the MVV in the PCR of blood samples (4).

There is no specific treatment or vaccines against the MVV, thus the control of the disease and the reduction of its prevalence must been done through the identification of infected animal in early stages of the disease and eradication of them (7, 8).

Differential diagnosis to the neurological form of MV include rabies, listeriosis, polioencephalomalacia, enzootic ataxia, and abscesses in the central nervous system. Respiratory form should be mainly differentiated from the ovine pulmonary adenocarcinoma (infection by Jaagsiekte sheep retrovirus), where the clinical signs are similar but histological lesions can be distinguished. Moreover, sheep with arthritis by the MVV should be differentiated by those caused by *Mycoplasma* spp. and *Chlamydia psittaci*. Meanwhile mastitis by MVV should be differentiated by chronic bacterial infections of the mammary gland (10).

References:

1. Benavides J, García-Pariente C, Fuertes M, Ferreras MC, García-Marín JF, Juste RA, Pérez V. Maedi-Visna: the Meningoencephalitis in Naturally Occurring Cases. J Comp Path 2019;140: 1-11.
2. Blacklaws BA. Small ruminant lentiviruses: Immunopathogesis of Visna-Maedi and caprine arthritis and encephalitis virus. Comp Immunol Microbiol Infect Dis 2012;35: 259-69.
3. Caswell JF, Williams KJ. Respiratory System: *Infectious respiratory diseases of sheep and goats* – viral diseases. In: Maxie MG, editor. Jubb, Kennedy & Palmer's Pathology of domestic animals. 6th Ed, Vol. 2. Philadelphia: Elsevier; 2016. p. 557-61.
4. Cechin RA, Perosa FF, Silva IG, Mendes RE, Baldi KRA, Pereira WAB, Gomes TMA. Diagnóstico de Maedi-Visna em Ovinos no Estado de Santa Catarina. Boletim de Diagnóstico do Laboratório de Patologia Veterinária (2013-2020) 2022;1: 69-80.
5. Gíslason G. Thaettir um innflutning búfjár og Karakúlsjúkdóma. Iceland Ministry of Agriculture Publ. Reykjavik, 1947: 235-54.
6. Pálsson PA. Maedi Visna. History and Clinical Description. In: Pétturson G, Hoff-Jorgensen R, editors. Maedi-Visna and Related Diseases. Developments in Veterinary Virology. Vol. 10. Norwell: Kluwer Academic Publishers; 1990. p. 3-74.
7. Pérez M, Biescas E, de Andrés X, Leginagoiboa I, Salazar E, Berriatua E, Reina R, Bolea R, de Andrés D, Juste RA. Visna/Maedi vírus serology in sheep: Survey, risk factors and implemenation of a successful control programme in Aragón (Spain). Vet J 2010;186; 221-5.
8. Peterhans E, Greenland T, Badiola J, Harkiss G, Bertoni G, Amorena B, Eliaszewicz M, Juste RA, Krassnig R, Lafont JP. Routes of transmission and consequences of small ruminant lentiviruses (SRLVs) infection and eradication schemes. Vet Res 2004;35: 257-74.
9. Siggurdsson B, Pállson P, Grímsson H. Visna, a demyelinating transmissible disease of sheep. J. Neiropathol Exp Neurol 1957;16: 389-403.
10. Simões SVD, Alcindo JF, Riet-Correa F. Lentiviroses de Pequenos Ruminantes. In: Riet-Correa F, Schild AL, Lemos R, Borges JR, Mendonça. Doenças de Ruminantes e Equídeos. 4th Ed, Vol. 1. São Paulo: MedVet; 2022. p. 130-43.

*The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation. These exercises are contributed by members and non-members from any country

of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the CL Davis website (https://davisthompsonfoundation.org/diagnostic-exercise/).

Editor for this Diagnostic Exercise: Saulo Pavarini

Editor-in-chief: Claudio Barros