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Toxic pneumopathy by *Trema micrantha* in sheep in the State of Santa Catarina, Brazil[1]

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ABSTRACT.- Quevedo L.S., Cristo T.G., Cunha A.L.O., Hemckmeier D., Marian L., Medeiros A.L.V., Pandolfo G.W. & Casagrande R.A. 2022. **Toxic pneumopathy by *Trema micrantha* in sheep in the State of Santa Catarina, Brazil**. *Pesquisa Veterinária Brasileira 42:e07128, 2022*. Laboratório de Patologia Animal, Departamento de Medicina Veterinária, Universidade do Estado de Santa Catarina, Av. Luís de Camões 2090, Conta Dinheiro, Lages, SC 88520-000, Brazil. E-mail: renata.casagrande@udesc.br

Poisoning by *Trema micrantha* commonly causes hepatocellular necrosis in cattle, sheep, and goats and edema and cerebral hemorrhage in horses. This plant can cause toxic pneumopathy in sheep, and there is only one report of the natural form and one of the experimental form in the State of Rio Grande do Sul. This study aimed to report an outbreak of the respiratory form of natural poisoning by *T. micrantha* in sheep. Six sheep developed clinical respiratory signs after consumption of the plant and four of them died and two recovered after treatment with dexamethasone. The sheep presented tachypnea, noisy breathing, edema of the face, eyelids, and vulva, and subcutaneous emphysema on the face and neck. Necropsy (Sheep 2, 3, and 4) showed uncollapsed, heavy, diffuse red lungs with evident costal impressions and a moderate amount of serosanguineous fluid flowed at section. The liver had a moderate diffuse evident lobular pattern. The histopathology of the lungs of the three necropsied sheep showed congestion and edema with the formation of hyaline membranes within accentuated diffuse alveoli, in addition to thickening of the alveolar septa due to mild to moderate diffuse type II pneumocyte hyperplasia and also mild to moderate diffuse infiltrate of macrophages, lymphocytes, plasma cells, and neutrophils in the lumen of alveoli, bronchi, and bronchioles. Sheep 3 also showed type II pneumocytes with enlarged and hyperchromatic nuclei, sometimes binucleated with evident nucleoli, and, in some regions, the pneumocytes were desquamated to the alveolar lumen forming small syncytia and mild multifocal hyperplasia in the bronchial epithelium. The anti-cytokeratin IHC evaluation showed marked diffuse intracytoplasmic staining in hyperplastic type II pneumocytes in the bronchiolar epithelium of the three evaluated sheep. The liver of the three sheep had mild multifocal centrilobular necrosis. It seems to be the second report of spontaneous poisoning by *T. micrantha* in sheep developing lung lesions described in Brazil and the first in the State of Santa Catarina.

INDEX TERMS: Toxic plant, pneumotoxicosis, *Trema micrantha*, sheep, interstitial pneumonia, hepatotoxic, Brazil.

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RESUMO.- [**Pneumopatia tóxica por *Trema micrantha* em ovinos no Estado de Santa Catarina, Brasil.**] A intoxicação por *Trema micrantha*, comumente causa em bovinos, ovinos e caprinos necrose hepatocelular e, edema e hemorragia cerebral em equinos. Essa planta em ovinos pode causar pneumopatia tóxica, existindo descrição apenas de um relato da forma natural e um da forma experimental no estado do Rio

Grande do Sul. O objetivo deste trabalho é relatar, um surto, da forma respiratória de intoxicação natural por *T. micranta* em ovinos. Seis ovinos desenvolveram sinais clínicos respiratórios após o consumo da planta e destes quatro morreram e dois após o tratamento com dexametasona se recuperaram. Os ovinos apresentaram taquipneia, respiração ruidosa, edema de face, pálpebras, vulva e enfisema subcutâneo na face e pescoço. Na necropsia (Ovinos 2, 3 e 4) observou-se pulmões não colabados, pesados, vermelhos difusos com impressões costais evidentes e ao corte fluindo moderada quantidade de líquido serosanguinolento. O fígado apresentava padrão lobular evidente difuso moderado. Na histopatologia, em pulmões dos três ovinos necropsiados havia congestão e edema com formação de membranas hialinas no interior de alvéolos difusos acentuados, além de espessamento dos septos alveolares devido a hiperplasia de pneumócitos tipo II difuso discreta à moderada, havia ainda, infiltrado de macrófagos, linfócitos, plasmócitos e neutrófilos difuso discreto a moderado no lúmen de alvéolo, brônquios e bronquíolos. No Ovino 3, observou-se ainda pneumócitos tipo II com núcleos aumentados e hipercromáticos, por vezes binucleados com nucléolos evidentes, e em algumas regiões estes pneumócitos estavam descamados para a luz alveolar formando pequenos sincícios e no epitélio de brônquios havia hiperplasia multifocal discreta. A avaliação IHQ anti-citoqueratina demonstrou marcação intracitoplasmática difusa acentuada em pneumócitos tipo II hiperplásicos no epitélio bronquiolar dos três ovinos avaliados. No fígado dos três ovinos havia necrose centrolobular multifocal discreta. Este parece ser o segundo relato da intoxicação espontânea por *T. micrantha* em ovinos desenvolvendo lesões pulmonares, descrito no Brasil e o primeiro no estado de Santa Catarina.

TERMOS DE INDEXAÇÃO: Planta tóxica, pneumotoxicose, *Trema micrantha*, ovinos, pneumonia intersticial, hepatotóxica, Brasil.

INTRODUCTION

Trema micrantha is a tree that measures between 5 and 12 meters and belongs to the family Ulmaceae; it has a trunk measuring between 20 and 40 centimeters in diameter, leaves with a rough upper surface and a pubescent lower surface that measure 7-10 centimeters in length and 3-4 centimeters in width (Lorenzi 1992). The leaves of the plant are considered palatable for cattle and easily consumed by animals, especially when there is a shortage of forage (Traverso et al. 2004), but *T. micrantha* is toxic to cattle (Traverso et al. 2004), goats (Traverso et al. 2003), sheep (Wouters et al. 2013a), and horses (Lorenzett et al. 2017).

There are two forms of poisoning by *T. micrantha*, the first is common in cattle, horses, and goats and is characterized by the accentuation of the lobular pattern of the liver (Traverso et al. 2003, 2004, Bandarra et al. 2010, Gava et al. 2010, Lorenzett et al. 2017), hemorrhages in the subcutaneous tissue, thyroid, and adrenal glands (Bandarra et al. 2010), in addition to cerebral edema and foci of hemorrhage in the thalamus of horses (Lorenzett et al. 2017). Jaundice and subcutaneous hemorrhages in the region of the scapula and sternum are described in goats, with an evident lobular, yellowish, friable pattern in the liver and edematous gallbladder and mesentery (Traverso et al. 2003). In addition to the aforementioned changes, petechiae and suffusions in the endocardium and all serosa of the organs of the abdominal cavity were reported in cattle, which also showed dry feces with mucus and blood, free clots in the abdominal cavity, edema and perirenal hemorrhage, and pale kidneys with multiple reddish spots in the cortical (Traverso et al. 2004). The main histological changes in this form consist of massive hepatocellular necrosis and marked centrilobular hemorrhage in cattle and goats (Traverso et al. 2003, 2004), whereas fibrinoid degeneration of blood vessels and edema, perivascular hemorrhage and multifocal thrombosis associated with marked neutrophilic infiltrate, and occasional lymphocytes, plasma cells, and macrophages can also be observed in horses (Lorenzett et al. 2017). In addition to liver damage, sheep also show Alzheimer type II astrocytes in the gray matter of the cerebral cortex, edema in the neuronal pericardium, and perivascular edema in the cervical segment of the spinal cord (Wouters et al. 2013a).

The second form of presentation has been described only in sheep, characterized by respiratory signs such as cyanosis, subcutaneous and mediastinal cervical emphysema, red lungs with rib demarcations, subepicardial hemorrhages, and accentuation of the lobular pattern of the liver (Wouters et al. 2013a, 2013b). The main change in these cases is observed in the lungs and is characterized by thickening of the alveolar septa due to diffuse proliferation of type II pneumocytes, in addition to thickening of the bronchiolar mucosa. There is only one report of the natural form and one of the experimental respiratory form in sheep (Wouters et al. 2013a, 2013b). This study aims to report what appears to be the second outbreak of the respiratory form of natural poisoning by *T. micrantha* in sheep.

MATERIALS AND METHODS

The epidemiological and clinical data of the disease were obtained from the producer and the veterinary doctor during a visit to the property. Four animals died naturally, three of them (Sheep 2, 3, and 4) undergoing necropsy by the veterinarian responsible for caring for the animals. Brain, spinal cord, trigeminal ganglion, pituitary gland, rete mirabile, heart, lung, pre-stomach, abomasum, kidney, bladder, liver, spleen, lymph node, and small and large intestine samples were collected in 10% buffered formalin for routine histopathological processing and hematoxylin and eosin (HE) staining.

Additionally, histological sections of the lungs were arranged on silanized slides for anti-cytokeratin immunohistochemistry (IHC) analysis (clone cocktail [AE1+AE3], 1:1000, Biocare Medical, LLC, Pacheco/CA, USA). Antigen retrieval was performed using moist heat in a pressure cooker (120°C) in citric acid solution (pH 6). The reaction signal was amplified using a peroxidase-conjugated polymer (Kit MACH 4 Universal HRP, Biocare Medical, LLC, Pacheco/CA, USA) and visualized with the chromogenic substrate 3,3′-diaminobenzidine (DAB, Dako, Glostrup, Denmark). Previously tested positive and negative controls were inserted into the reactions.

RESULTS

The property is located in the municipality of Pouso Redondo, region of Alto Vale do Itajaí, in the State of Santa Catarina, Brazil. The herd consisted of 20 Santa Inês, Dorper, and crossbred Santa Inês sheep aimed at the commercialization of lambs. The animals were allocated in three hectares, submitted to semi-extensive management. The animals were maintained in a sheepfold at night. The diet consisted of native grassland and oat and ryegrass pastures in the winter and millet in the

summer. The sheep were supplemented with ground corn and species-specific salt when collected at night.

Six sheep developed clinical respiratory signs and four of them evolved to death (Sheep 2, 3, and 4). The first adult female crossbred Santa Inês (Sheep 1) developed edema of the eyelids, vulva, and subcutaneous emphysema on the face and neck, and died before veterinary care. Necropsy could not be performed due to the marked degree of autolysis. Two days after treatment, the second Santa Inês sheep, approximately 5 years old (Sheep 2), presented edema of the face, eyelids, bloat, and was found dead. Another 3-year-old male Dorper was found dead (Sheep 3), and a 2-year-old female crossbred Santa Inês (Sheep 4) died two days later. Two other adult crossbred Santa Inês females (Sheep 5 and 6) presented respiratory signs characterized by tachypnea, noisy breathing, and were medicated with dexamethasone (0.2mg/kg) and penicillin (10000IU/kg), both intramuscularly twice a day for four and five days, respectively. These animals had a good response to treatment with clinical recovery.

Fig.1. Poisoning by *Trema micrantha* in sheep in Santa Catarina, Brazil. Branches of *T. micrantha* in the paddock for sheep raising after pruning in front of the sheepfold.

One day after the onset of clinical signs in Sheep 1, the owner revealed that he had sowed oat and ryegrass seeds and used branches of *Trema micrantha* to cover the seeds and spread them. The branches were left in front of the sheepfold, where the plant was consumed by the sheep (Fig.1). Sheep 2 died three days after the first contact with the plant and Sheep 3 and 4 five days later.

At necropsy, the three Sheep (2, 3, and 4) that died spontaneously presented non-collapsed, heavy, diffuse red lungs with evident costal impressions (Fig.2). and a moderate amount of serosanguineous fluid flowing at section, in addition to subpleural petechiae Sheep 3 and 4 developed emphysema in the cervical and cranial thoracic regions. A slight amount of serous fluid was observed in the pericardial sac of Sheep 4. The three sheep showed the liver with an evident moderate diffuse lobular pattern (Fig.3).

On histopathology, the lungs of the three sheep showed congestion and edema with the formation of hyaline membranes within accentuated diffuse alveoli, in addition to thickening of the alveolar septa due to mild to moderate diffuse type II pneumocyte hyperplasia (Fig.4). There was a mild to moderate diffuse infiltrate of macrophages, lymphocytes, plasma cells, and neutrophils in the lumen of the alveoli, bronchi, and bronchioles. Sheep 3 also showed type II pneumocytes with enlarged and hyperchromatic nuclei, sometimes binucleated with evident nucleoli, and, in some regions, the pneumocytes were desquamated to the alveolar lumen forming small syncytia and mild multifocal hyperplasia in the bronchial epithelium. The anti-cytokeratin IHC evaluation showed marked diffuse intracytoplasmic staining in hyperplastic type II pneumocytes (Fig.5) in the bronchiolar epithelium of the three evaluated sheep.

The liver of the three sheep had mild multifocal centrilobular necrosis. Sheep 2 and 4 had moderate diffuse hepatocellular degeneration in the midzonal and portal regions.

Hydropic degeneration in the superficial layer of the discrete multifocal mucosa (Sheep 2 and 3) was also observed in the rumen. The kidneys had moderate hyaline casts in the multifocal tubular lumen (Sheep 4). The other evaluated organs did not observe histological changes.

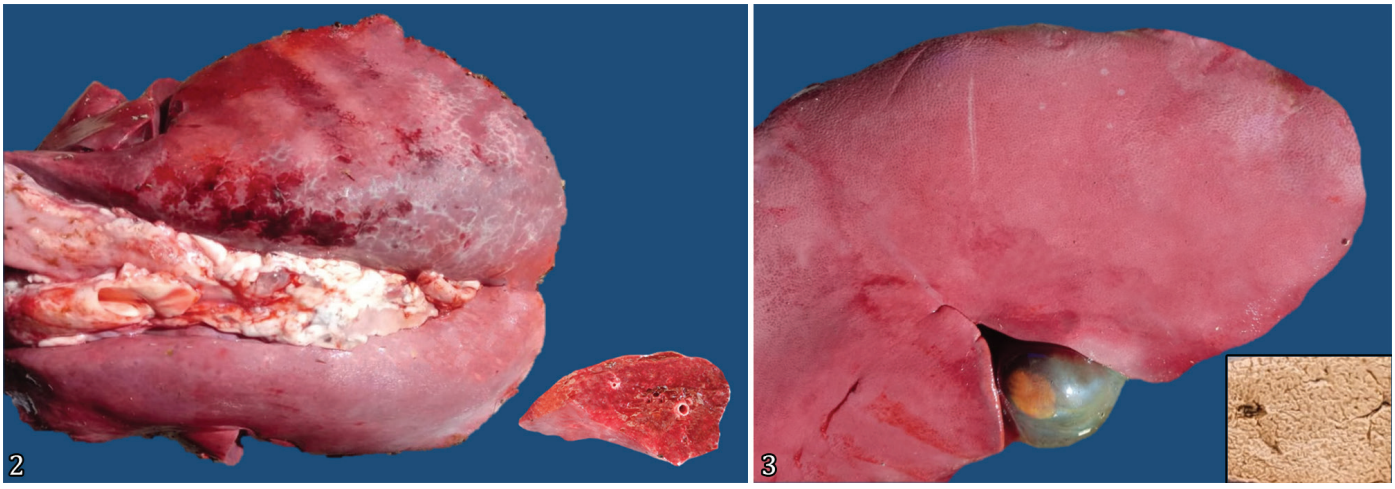

Fig.2-3. Poisoning by *Trema micrantha* in sheep in Santa Catarina, Brazil. (**2**) Lung: non-collapsed, heavy, diffuse red lungs with evident costal impressions. In the detail of the lung cross section. (**3**) Liver: markedly evident lobular pattern. In the detail of the transverse section of the liver fixed in 10% buffered formalin.

DISCUSSION

Cases of poisoning by consumption of leaves from trees or shrubs follow the same epidemiological pattern and may occur when producers perform pruning and the remains of branches are kept in the paddocks or fed to animals, or when storms cause trees or branches to fall and the animals have access to them (Tokarnia et al. 2012, Wouters et al. 2013b). In the present study, the producer was unaware of the risk of poisoning, and after sowing seeds, he deposited the branches in front of the sheepfold, which facilitated the animals' access to the leaves of *Trema micrantha*, easily ingested due to its palatability (Traverso et al. 2004).

Experimentally, the toxic dose of *T. micrantha* for sheep in the hepatic form varies from 20 to 50g/kg of live weight, with 20g/kg being the minimum dose for clinical disease to occur with consequent recovery, and 25g/kg the minimum dose to cause death (Wouters et al. 2013a). Doses of 20, 22.5, and 35g/kg (total 77.5g/kg) or 22.5, 30, and 50g/kg (total 102.5g/kg) during an interval of 30 days can cause poisoning, with the development of lung lesions (Wouters et al. 2013b). In an experimental study, the supply of *T. micrantha* to a sheep led to the development of clinical signs at the first dose (20mg/kg), characterized by tachypnea, severe dyspnea, cyanotic mucous membranes, and mucus discharge from the nostrils with improvement, and this and another sheep died within 4-5 days after the last dose (Wouters et al. 2013b). The three animals in this report showed similar signs of pneumotoxicosis with evolution between one and five days until death. This clinical history and evolution are lower than the spontaneous cases described in the literature, with an evolution of 11 days, but the clinical signs were similar (Wouters et al. 2013b). In the present study, the amount ingested by each animal could not be measured since the sheep consumed the plant spontaneously.

The active principle of *T. micrantha* is not yet clearly defined (Matos et al. 2011, Wouters et al. 2013b), but there is a comparison with *Trema tomentosa* var. *aspera*, which is commonly found in the coastal regions of southeastern and northwestern Australia and on the island of New Guinea. Sheep and cattle easily consume its leaves, which have trematoxin as an active ingredient, which is a glycoside toxic to liver tissue and can lead to hepatocellular necrosis at doses of 12-15mg/kg (Oelrichs 1968). Thus, the glycoside is metabolized by the rumen microbiota and/or liver detoxification (Cullen & Brown 2012).

Although the toxic principle is unknown, the intermediate metabolites can lead to lung injuries such as damage to the alveolar and bronchiolar epithelium, which subsequently lead to loss of blood-air barrier integrity (Wouters et al. 2013a). Changes in the respiratory form after ingestion of the plant probably start causing damage to type I pneumocytes of alveoli and, consequently, lead to increased vascular permeability, formation of hyaline membranes, and proliferation of type II pneumocytes (Wouters et al. 2013b). Edema and emphysema described in a report from Rio Grande do Sul are associated with increased intra-alveolar pressure as a result of increased expiratory effort and altered interstitial permeability (Wouters et al. 2013b). The main macroscopic finding was observed in the lungs, evidenced by microscopy, and confirmed by IHC, characterized by thickening of alveolar septa due to proliferation of type II pneumocytes and bronchiolar epithelium characteristic of poisoning by *T. micrantha* (Wouters et al. 2013a, 2013b).

The microscopic lesions observed in the lungs of sheep in this outbreak are compatible with those described in the outbreak in Rio Grande do Sul (Wouters et al. 2013b), alterations such as proliferation of type II pneumocytes and formation of syncytial cells, which may be present in intoxication. In cases of *Crotalaria pallida* poisoning, clinical signs are characterized by increased respiratory rate and abdominal breathing, in addition to similar macroscopic lesions (Borelli et al. 2016), can be considered differentials of *T. micrantha* poisoning. However, it is easily distinguishable under microscopy, in cases of *C. pallida* poisoning, the lesions are characterized by edema on the pleural surface, pleural spaces and around the peribronchial and peribronchiolar arteries (Borelli et al. 2016) without involvement of the type II pneumocyte, characteristic of the current outbreak, which may contribute to the definitive laboratory diagnosis.

The differential diagnosis of poisoning by *T. micrantha* must be performed by excluding other causes that co-occur with interstitial pneumonia. Fog fever usually occurs in adult cattle transferred from dry pastures to lush pastures (rich in L-tryptophan) during autumn (Wicpolt et al. 2014). Fog

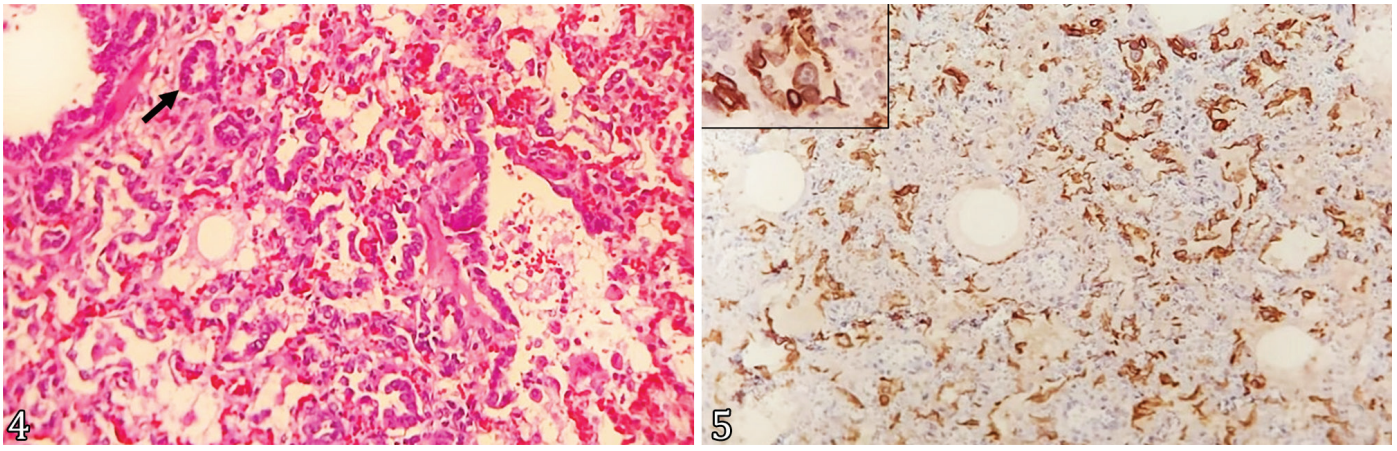

Fig.4-5. Poisoning by *Trema micrantha* in sheep in Santa Catarina, Brazil. (**4**) Lungs: thickening of the alveolar septa due to type II pneumocyte hyperplasia (arrow). HE, obj.20x. (**5**) Lungs: marked diffuse intracytoplasmic staining in hyperplastic type II pneumocytes. Anti-cytokeratin IHC, obj.20x. Inset: closer image of a hyperplastic type II pneumocyte. Anti-cytokeratin IHC, obj.100x.

fever can be ruled out due to the pasture conditions at the site because the dry period deteriorated the pasture, hampering its development, not being possible to offer it to the animals. Poisoning by sweet potato (*Ipomoea batatas*) contaminated by the fungus *Fusarium solani* and *Fusarium oxysporum* is another important cause of interstitial pneumonia (Fighera et al. 2003). In sheep, *C. pallida* can cause acute pneumotoxicosis at a dose of 2.5g/kg (Borelli et al. 2016). Epidemiology, in this case, was important to rule out these intoxications, given that the property did not have lush pastures and the animals did not have access to *I. batatas* or *C. pallida*.

Some viral causes must also be considered in the differential diagnosis, such as bluetongue virus infection that also occurs in Santa Catarina (Quevedo 2018) which causes edema, hyperemia, occasional foci of hemorrhage, in addition to the formation of hyaline membranes, emphysema on the edges and edema of the interlobular septa (Antoniassi et al. 2010). Infection such *Lentivirus*, which leads to the development of Maedi-Visna disease in sheep, which develops interstitial pneumonia (Pinczowski et al. 2017). Another infectious disease to be ruled out is pulmonary adenomatosis, which is caused by the Jaagsiekte sheep retrovirus (JSRV), characterized by forming papillary or acinar adenocarcinoma (García-Goti et al. 2000). In these cases, the exclusion was performed by epidemiology and histological findings.

This was the main change that occurred in the present case and considered uncommon since only one spontaneous case of pneumotoxicosis caused by consumption of *T. micrantha* was described in Rio Grande do Sul with morbidity and mortality of 100% (2/2 sheep) (Wouters et al. 2013b). In the present report, six sheep developed clinical signs and four of them died. Thus, there was a mortality of 66.7%, possibly due to the treatment performed by the veterinarian, which proved to be efficient. In an outbreak of *C. pallida* poisoning, mortality reached 12.4% in a herd of 186 sheep in Santa Catarina (Borelli 2015). Generally, in these cases of acute intoxication, therapeutic treatment is not implemented, however, in this case the recommended treatment with dexamethasone was effective. Dexamethasone has as its mechanism of action the direct inhibition of the B cell nuclear factor kappa, production of proteins such as tumor necrosis factor alpha (TNF-α), IL-6 and IL-8, and macrophage colony-stimulating factor and protein activator 1 (induction of several genes, pro-inflammatory interleukins and the enzyme cyclooxygenase - COX) (Jericó & Marco 2017). This glucocorticosteroid is used in the treatment of hemorrhagic or septic shock by maintaining the integrity of the microvasculature, inhibiting cytotoxicity and acting on free radicals, in addition, they are used in the treatment of cerebral edema and inflammatory reactions (Jericó & Marco 2017). Possibly due to the anti-inflammatory factor of dexamentasone, there was a reduction in pulmonary edema in sheep, the treatment performed quickly was important to the recovery of animals that developed respiratory clinical signs. It is noteworthy that after starting treatment with dexamethasone, there was no further mortality.

The trematoxin isolated from *Trema tomentosa* var. *aspera* seems to act as a hepatic toxin leading to the accentuation of the lobular pattern in sheep, as observed in the present study to a lesser extent (Mulhearn 1942, Oelrichs 1968). In horses, this glycoside causes severe hepatocellular necrosis (Hill et al. 1985, Bandarra et al. 2010, Lorenzett et al. 2017).

Some plants also cause acute liver necrosis, such as *Cestrum axillare*, *Cestrum parqui*, *Cestrum corymbosum*, *Cestrum intermedium*, *Sessea brasiliensis*, *Vernonia mollissima*, *Vernonia rubricaulis*, *Xanthium* sp., and *Dodonaea viscosa* (Riet-Correa et al. 1986, Chaulet et al. 1990, Gava et al. 1991, Marinho et al. 2018, Soares et al. 2018, Barbosa et al. 2020, Pohl et al. 2021, Zamboni et al. 2021). These plants were not found on the property, allowing excluding them from the diagnosis, demonstrating the importance of an effective epidemiological study in these cases.

Vascular changes characterized by subcutaneous petechiae and hemorrhages in the thyroid and adrenal glands have been reported in horses, in addition to bloody content in the lumen of the small intestine (Bandarra et al. 2010). In the brain, yellowish areas with friable multifocal to grayish to dark red coalescing foci can be observed mainly in the rhombencephalon, diencephalon, telencephalon, mesencephalon, and striatum, with the most severe lesions being in the pons (Lorenzett et al. 2017). Spinal cord injuries (mostly in lumbar swelling) with edema and depressed dark areas in the dorsal and ventral horns are also reported, and the gray matter may be friable and yellowish in the sacral region of the equine species (Lorenzett et al. 2017). In histopathology, spinal cord injuries consist of severe vasculitis and liquefactive necrosis of white and gray matter (brainstem, cerebellum, and spinal cord), characterized by transmural multifocal fibrinoid necrosis of blood vessels, sometimes occluded by thrombi and associated with perivascular hemorrhage and severe myelin vacuolization (Lorenzett et al. 2017). The lesions observed in the equine brain and spinal cord due to hepatic encephalopathy were not observed in the present study.

CONCLUSION

This seems to be the second report of an outbreak of spontaneous poisoning by *Trema micrantha* in sheep developing lung lesions described in Brazil and the first report in the State of Santa Catarina. The diagnosis of poisoning by *T. micrantha* was determined from the epidemiology together with the clinical signs associated with necropsy, histopathological, and immunohistochemical findings.

Conflict of interest statement.- The authors declare that there are no conflicts of interest.

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