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ASPECTOS CLÍNICOS E PATOLÓGICOS DA INTOXICAÇÃO ESPONTÂNEA POR *SENECIO* SPP. EM RUMINANTES NO RIO GRANDE DO SUL

DISSERTAÇÃO DE MESTRADO

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Santa Maria, RS, Brasil
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Dissertação apresentada ao Curso de Mestrado do Programa de Pós-graduação em Medicina Veterinária, Área de concentração em Patologia e Patologia Clínica, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para a obtenção do grau de
Mestre em Medicina Veterinária

Orientador: Claudio S. L. Barros

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elaborada por
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como requisito parcial para obtenção do grau de
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RESUMO

Dissertação de Mestrado
Programa de Pós-graduação em Medicina Veterinária
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ASPECTOS CLÍNICOS E PATOLÓGICOS DA INTOXICAÇÃO ESPONTÂNEA POR *SENECIO* SPP. EM RUMINANTES NO RIO GRANDE DO SUL

AUTORA: Paula Roberta Giaretta
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Santa Maria, 18 de dezembro de 2014

Durante um período de 24 meses foram realizadas visitas periódicas a propriedades de bovinocultura de corte no Rio Grande do Sul, onde havia a suspeita de intoxicação por *Senecio* spp. Na primeira parte desta dissertação, relata-se a ocorrência de um surto de intoxicação natural por *Senecio brasiliensis* em bovinos em que o principal sinal clínico observado foi fotossensibilização. O surto ocorreu em setembro de 2013, acometendo vacas adultas que permaneceram durante os seis meses anteriores em um campo de 205 hectares com abundante infestação por *Senecio brasiliensis*. Fotossensibilização foi observada em 83 vacas de um total de 162 (51,3%). Realizou-se biópsia hepática em todas as vacas do rebanho e três vacas doentes foram necropsiadas. Os principais achados histopatológicos decorrentes de intoxicação por *Senecio brasiliensis* nos bovinos biopsiados foram fibrose hepática, megalocitose e proliferação de ductos biliares, observados em 119 animais. Seis vacas testadas apresentaram aumento da atividade sérica da gama glutamil transferase. Na segunda parte da dissertação, foi realizado um estudo de um surto de intoxicação por *Senecio* spp. em ovinos em 2014, dando-se ênfase aos aspectos morfológicos para o estabelecimento do diagnóstico da intoxicação nessa espécie. Dez ovelhas adultas de um rebanho de 860 ovinos morreram com sinais da doença e oito que estavam doentes foram eutanasiadas e necropsiadas. Os sinais clínicos incluíam emagrecimento, apatia e fotossensibilização. Quatro ovelhas, de um total de sete que foram testadas, apresentaram aumento da atividade sérica da gama glutamil transferase e duas apresentaram fosfatase alcalina sérica elevada. Na necropsia, em três dos oito ovinos necropsiados, o fígado estava levemente mais firme, com superfície capsular ligeiramente irregular e com nódulos pálidos na superfície de corte. Em outros três ovinos o fígado era macroscopicamente normal. Em dois dos oito ovinos necropsiados a cápsula de Glisson era brancacenta devido à fibrose, e parcialmente aderida ao diafragma. Histologicamente, as principais alterações observadas, que contribuíram para o estabelecimento do diagnóstico de intoxicação crônica por alcaloides pirrolizidínicos nas ovelhas deste surto foram hepatomegalocitose, proliferação de ductos biliares e fibrose. Todas as ovelhas apresentavam degeneração esponjosa grave no cerebelo e pedúnculos cerebelares, ponte, mesencéfalo e tálamo. Sugere-se que esses sejam os sítios anatômicos de eleição no encéfalo para a observação dessa lesão em ovinos com intoxicação por *Senecio* spp.

Palavras-chave: Alcaloides pirrolizidínicos. Patologia. *Senecio*. Intoxicações por plantas. Doenças de bovinos. Doenças de ovinos.

ABSTRACT

MSc Dissertation
Programa de Pós-Graduação em Medicina Veterinária
Universidade Federal de Santa Maria, RS, Brasil

CLINICAL AND PATHOLOGICAL ASPECTS OF CHRONIC *SENECIO* SPP. POISONING IN RUMINANTS IN RIO GRANDE DO SUL

AUTHOR: Paula Roberta Giaretta
ADVISER: Claudio S. L. Barros
Santa Maria, December 18, 2014

During 36 months a study was conducted in beef cattle farms in Rio Grande do Sul, Brazil to survey outbreaks of *Senecio* spp. poisoning. The first part of this dissertation reports an outbreak of *Senecio brasiliensis* poisoning in cows where the main clinical sign was photosensitization. Adult cows that were placed during six months in a 205-hectare pasture heavily infested by *Senecio brasiliensis* were affected in September, 2013. Photosensitization was seen in 83 out 162 cows. Liver biopsy was performed in all cows under risk and three cows were necropsied. Histopathological findings in the liver related to pyrrolizidine alkaloids toxicosis consisted of fibrosis, megalocytosis and biliary ductal proliferation and were present in 119 of the biopsied cows. Six tested cows had increased serum activity of gamma glutamyl transferase. In the second part of this dissertation, a study of an outbreak of seneciosis in sheep in 2014 is reported. Morphological aspects considered important for the establishment of diagnosis in this species were stressed. Ten out of 860 adult sheep with clinical signs of seneciosis died spontaneously and eight sick ewes were euthanized and necropsied. Clinical signs included weight loss, apathy and photosensitization. Four out of seven tested sheep presented increased serum levels of gamma glutamil transferase and two had elevated alkaline phosphatase serum activity. At necropsy, three out of eight ewes presented slightly irregular toughened livers with multifocal nodules, two out of eight ewes had a whitish liver with thickened fibrotic Glisson's capsule partially adhered to the diaphragm, and three out of eight ewes had smooth and grossly normal livers. Histologically, the main hepatic findings that allowed for the establishment of the diagnosis were megalocytosis, proliferation of bile ducts and fibrosis. Spongy degeneration was observed in the brains of all eight necropsied sheep and was more severe at the cerebellar peduncles, mesencephalon, thalamus, and pons. These are suggested as the portions of election to investigate microscopic lesions of hepatic encephalopathy in sheep with chronic seneciosis.

Key words: Pyrrolizidine alkaloids. Pathology. *Senecio*. Plant poisoning. Diseases of cattle. Diseases of sheep.

SUMÁRIO

1. INTRODUÇÃO

As intoxicações por plantas são responsáveis por grandes perdas econômicas relacionadas com a morte de animais de produção no Brasil, sendo consideradas tão importantes quanto a raiva e o botulismo (TOKARNIA, DOBEREINER, PEIXOTO, 2002). Estima-se que mais de 820.000 bovinos e 399.000 ovinos morram anualmente devido a intoxicações por plantas no país (PESSOA, MEDEIROS, RIET-CORREA, 2013).

A ingestão de plantas do gênero *Senecio* spp. é responsável por mais de 50% das mortes de bovinos causadas por plantas tóxicas no Rio Grande do Sul (RIET-CORREA, MEDEIROS, 2001; RISSI et al., 2007). Neste gênero, da família Asteraceae, estão incluídas mais de 1.200 espécies (TOKARNIA et al., 2012). No Brasil são conhecidas 67 delas, com distribuição geográfica na região centro-sul do país (HIND, 1993). A espécie mais frequente nessa região é *S. brasiliensis,* conhecida pelos nomes populares de maria-mole e flor-das-almas (MOTIDOME, FERREIRA, 1966). No Rio Grande do Sul, as espécies tóxicas de *Senecio* são plantas anuais, florescem a partir do mês de outubro e apresentam flores amarelas (TOKARNIA et al., 2012), com exceção de *S. tweediei* e *S. bonariensis*, que possuem flores brancas (MÉNDEZ, RIET-CORREA, 1993; MATZENBACHER, 1998). Estas plantas comportam-se como invasoras de culturas e pastagens nativas (TOKARNIA et al., 2012).

No Rio Grande do Sul, a doença em bovinos foi diagnosticada em áreas invadidas por *S. brasiliensis*, *S*. *selloi* (BARROS et al., 1987; MÉNDEZ, RIET-CORREA, SCHILD, 1987), *S. cisplatinus*, *S*. *heterotrichius*, *S. leptolobus* (MÉNDEZ et al., 1987), *S*. *oxyphyllus* (BARROS, METZDORF, PEIXOTO, 1992; DRIEMEIER, BARROS, 1992), *S*. *tweediei* (MÉNDEZ, RIET-CORREA, 1993) e *S. madagascariensis* (CRUZ et al., 2010; STIGGER et al., 2014). Em Santa Catarina, a intoxicação é causada pela ingestão de *S*. *brasiliensis* (MÉNDEZ, 1993). A intoxicação pode ocorrer também pela ingestão acidental da planta com feno (FOWLER, 1968; DRIEMEIER, BARROS, PILATI, 1991; BARROS, METZDORF, PEIXOTO, 1992; BARROS et al., 2007) e silagem contaminados; nessa última registra-se uma perda de 20% a 30% no conteúdo de alcaloides pirrolizidínicos de *Senecio* spp. (MÉNDEZ, 1993).

Plantas do gênero *Senecio* contêm como princípio tóxico os alcaloides pirrolizidínicos, que provocam lesão hepática progressiva, podendo observar-se os sinais clínicos da doença vários meses após a ingestão (BULL, CULVENOR, DICK, 1969; TOKARNIA et al., 2012). As mortes dos bovinos acontecem de forma esporádica durante um período prolongado de tempo, podendo ocorrer durante o ano todo (GRECCO et al., 2010; KARAM, MOTTA, 2011). Na maioria dos surtos, as mortes são mais frequentes de agosto a fevereiro (BARROS et al., 1987; MÉNDEZ, RIET-CORREA, SCHILD, 1987; DRIEMEIER, BARROS, PILATI, 1991; BARROS, METZDORF, PEIXOTO, 1992). As espécies do gênero *Senecio* são pouco palatáveis e são consumidas pelos bovinos somente sob determinadas condições. A ingestão provavelmente ocorre durante os meses de maio a julho, período em que as diferentes espécies estão em brotação, com maior concentração de alcaloides e a disponibilidade de forragem é escassa (MÉNDEZ, RIET-CORREA, 2008). Provavelmente, em razão de fatores climáticos, o início da brotação varia grandemente de um ano para outro. Em alguns anos o número de surtos é maior, provavelmente devido a variações na quantidade de *Senecio* spp., à época do início da brotação e/ou à carência maior de forragem no inverno, o que induziria a um consumo excessivo da planta. Em algumas ocasiões o aparecimento dos sinais clínicos parece estar associado ao estresse, o que foi observado em surtos no outono, época de severa estiagem, afetando bovinos que tinham ingerido a planta no ano anterior (SCHILD et al., 1989).

A intoxicação geralmente ocorre em pastagens onde não existe ovinos, espécie que nas condições da região, geralmente consome e controla a planta sem adoecer (BARROS et al., 1987; DRIEMEIER, BARROS, PILATI, 1991; BARROS, METZDORF, PEIXOTO, 1992). São afetados bovinos de diversas categorias, mas, devido à evolução crônica da doença, adoecem preferentemente vacas, por serem aquelas que permanecem mais tempo no estabelecimento. A morbidade é variável entre 1% e 30%, e a letalidade é praticamente 100% (BARROS et al., 1987; MÉNDEZ, RIET-CORREA, SCHILD, 1987; DRIEMEIER, BARROS, PILATI, 1991; BARROS, METZDORF, PEIXOTO, 1992).

A intoxicação é mais rara em ovinos, mas foi diagnosticada nessa espécie em dois surtos no Rio Grande do Sul (ILHA et al., 2001; GRECCO et al., 2011). A intoxicação por *Senecio* foi descrita também em equinos, no Estado de São Paulo (CARVALHO, MAUGÉ, 1946), Paraná (CURIAL, GUIMARÃES, 1958), Santa

Catarina e Rio Grande do Sul (GAVA, BARROS, 1997). Há a descrição de um surto de intoxicação por *Senecio brasiliensis* em búfalos no Rio Grande do Sul (CORRÊA et al., 2008).

O objetivo desse trabalho é determinar as características epidemiológicas e os métodos de diagnóstico que podem auxiliar na prevenção de surtos e apresentar os achados clínicos e patológicos em ruminantes com intoxicação por *Senecio* spp. no Rio Grande do Sul. Desse estudo resultaram dois trabalhos científicos. A Introdução, Material e Métodos, Resultados e Discussão obtidos desses dois trabalhos são incluídos na íntegra a seguir.

1. ARTIGO 1

Seneciosis in cattle associated with photosensitization

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1º. TRABALHO

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Seneciosis in cattle associated with photosensitization[1]

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ABSTRACT.- Giaretta P.R., Panziera W., Galiza G.J.N., Brum J.S., Bianchi R.M., Hammerschmitt M.E., Bazzi T. & Barros C.S.L. 2014. **Seneciosis in cattle associated with photosensitization.** *Pesquisa Veterinária Brasileira 34(5):427-432.* Laboratório de Patologia Veterinária, Departamento de Patologia, Universidade Federal de Santa Maria, Camobi, Santa Maria, RS 97105-900, Brazil. E-mail: claudioslbarros@uol.com.br

Senecio spp. poisoning is the main cause of cattle mortality in the central region of Rio Grande do Sul. This paper reports an outbreak of seneciosis in cattle with high prevalence of photosensitization, where 83 out of 162 cows (51.3%) presented this clinical sign. The outbreak occurred in September 2013, affecting adult cows that were held in a 205 hectare-pasture from April to October 2013 with abundant *Senecio brasiliensis* infestation. Main clinical signs were weight loss, excessive lacrimation or mucopurulent ocular discharge, nasal serous discharge, ventral diphteric glossitis, crusts in the nose, teats, dorsum of ears, and vulva. Liver biopsy was performed in all the cows under risk and three affected cows were necropsied. Histopathological findings in the liver consisted of fibrosis, megalocytosis, and biliary ductal proliferation. Characteristic hepatic histological changes were present in 73.4% of the biopsied animals. Six cows had increased serum activity of gamma glutamyl transferase. The main necropsy findings were a hard liver, distended gall bladder, edema of the mesentery and abomasum. Liver histological changes in the necropsied cows were similar to those of the biopsied livers. Spongy degeneration was detected in the brain of necropsied cows and is characteristic of hepatic encephalopathy.

INDEX TERMS: Poisonous plants, *Senecio brasiliensis*, Asteraceae, photosensitization, liver, seneciosis, plant poisoning, cattle disease.

RESUMO.- [**Seneciose em bovinos associada a fotossensibilização**.] A intoxicação por plantas do gênero *Senecio* é a principal causa de morte de bovinos na região central do Rio Grande do Sul. Neste trabalho, relata-se um surto de intoxicação por *Senecio brasiliensis* em bovinos com alta prevalência de fotossensibilização, onde 83 vacas de um total de 162 (51,3%) apresentaram esse sinal clínico. O surto ocorreu em setembro de 2013, acometendo vacas adultas que foram colocadas em um campo de 205 hectares com abundante infestação por *Senecio brasiliensis* de abril a outubro de 2013. Os principais sinais clínicos foram emagrecimento, lacrimejamento excessivo ou secreção ocular mucopurulenta, secreção nasal serosa, glossite diftérica ventral e crostas no plano nasal, tetos, ponta das orelhas e na vulva. Realizou-se biópsia hepática em todas as vacas do rebanho e três vacas doentes foram necropsiadas. Os principais achados histopatológicos dos bovinos biopsiados foram fibrose hepática, megalocitose e proliferação de ductos biliares. As lesões hepáticas foram observadas em 73,4% dos bovinos biopsiados. Seis vacas testadas apresentaram aumento da atividade sérica da gama glutamil transferase. Nas vacas necropsiadas, o fígado era firme, a vesícula biliar distendida e havia edema do mesentério e do abomaso. As lesões histológicas observadas nos fígados dos bovinos necropsiados eram semelhantes às dos fígados biopsiados. Espongiose foi detectada no cérebro das vacas necropsiadas e é uma lesão característica de encefalopatia hepática.

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TERMOS DE INDEXAÇÃO: Plantas tóxicas, *Senecio brasiliensis*, Asteraceae, fotossensibilização, fígado, seneciose, intoxicação por plantas, doenças de bovinos.

INTRODUCTION

Seneciosis is a chronic hepatotoxicosis of livestock caused by the ingestion of *Senecio* spp. plants that contain pyrrolizidine alkaloids (Kellerman et al. 2005). It is the main cause of death in adult cattle in Southern Brazil (Barros et al. 1992, Rissi et al. 2007). A survey in the files of our laboratory confirm that statement, since in 6.706 recorded necropsies of cattle *Senecio* spp. poisoning accounted for over 50% of the deaths caused by plants poisoning (Lucena et al. 2010).

Two most important texts on plant poisonings in livestock (Kellerman et al. 2005, Tokarnia et al. 2012a) classify *Senecio* spp. as plants that cause hepatoxicosis without causing photosensitization, or infrequently causing it, a statement which is in accordance with our previous observations (Barros et al. 1992).

The purpose of this paper is to report a large outbreak of seneciosis in cattle in which the main clinical sign was photosensitivity.

MATERIAL AND METHODS

Data for this report were obtained during five on-site visits to the farm where the problem occurred. During these visits the pastures were observed in detail and all the cows under risk were clinically examined. Six affected cows were bled for liver function tests (aspartate aminotransferase [AST], gamma glutamyl transferase [GGT], alkaline phosphatase [AP]), and complete red cell count. Liver biopsy was performed in all 162 cows according to previously described (Barros et al. 2007). Necropsies were performed in three affected cows from which several tissues were sampled and routinely processed for histopathology. Plant specimens were sent to Botanic Department at *Universidade Federal de Santa Maria* for classification.

RESULTS

The outbreak occurred in a farm located in the municipality of São Sepé, Rio Grande do Sul, Brazil (30º09'38" South, 53º33'55" West, 85 meters above sea level). The population under risk consisted of 162 pregnant cows which were impregnated in November/December, 2012. In April/May, 2013 the 162 cows were placed in 205 hectare-pasture (Pasture 1) where they were additionally fed rice stubs hay and proteinated salt supplement[5]. In October 3, 2013 the 162 cows were moved to another pasture (Pasture 2) that used to be a soybean crop which had been harvest in April that year. The cows stayed in Pasture 2 until October 23, 2013. The majority of the 162 cows calved between August and September 2013. On late September a disease characterized by weight loss and photosensitization was noted affecting several cows which were then moved to another pasture (Pasture 3).

The grass of Pasture 1 consisted almost exclusively of South African lovegrass (*Eragrostis plana* Nees) or, as it is named in Brazil, capim-annoni. *Senecio brasiliensis* (Fig.1) was abundant in part (about 85 hectares) of Pasture 1. No known toxic plants were observed either in Pasture 2 or 3. Dry soybean stubs were abundant in Pasture 1.

The first sick cows were observed in the second half of September 2013. Main observed clinical signs were weight loss and photosensitization. By October 25, 2013, when liver biopsy was carried out in the 162 cows under risk, it was estimated that loss of weight was 50-80 kg per affect cow although some affected cows that subsequently died with acute clinical signs were in good body condition.

Clinical findings of photosensitization included photophobia, excessive lacrimation or mucopurelent ocular discharge (Fig.2), and nasal serous discharge which provoked a continuous licking of the nose (Fig.3) resulting in ventral diphteric glossitis (Fig.4) due to persistent exposure of the ventral surface of the tongue to sunlight. Skin lesions were frequently seen in the nose (Fig.5), teats (Fig.6), dorsum of ears (Fig.7), vulva and vagina (Fig.8), and over the tuberosity of the ischium. The initial lesions were edematous and erythematous with fluid oozing through the affected skin to form crusts. Those then progressed and within 15-30 days the necrotic skin became dry and parchment-like. These portions of sloughed off imparting to the lesion an aspect of the bark of a tree (Fig.9). Some of the cows that died presented behavioral changes. They presented compulsive aimless walking, mania and seek water ponds and woods.

Serum activity of GGT was increased in six affected cows that were tested, with values varying from 181-799 U/L (reference values: 6,1-17,4 U/L). All the other hematological and serological parameters tested were within normal limits.

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[5]Presencefós. In Vivo Nutrição e Saúde Animal Ltda, Rua Guilherme Schell, 10.780, Canoas, RS 92420-000, Brazil.

Lesions found at necropsy of two affected cows were essentially similar. There were striking edema of the mesentery, ascites, and marked distension of the gallbladder. The liver was diffusely firm and had a multinodular cut surface in two cows and a smooth appearance in another one.

Histologically, in biopsied and necropsied cows there was disruption of hepatic architecture, where the cords and lobules were dissected by abundant connective tissue and fibroblasts. Remaining hepatocytes had vacuolated cytoplasm and appeared to form nodules surrounded by connective tissue (Fig.10). Enlarged hepatocytes (megalocytosis) were seen mainly in periportal areas (around five megalocytes by high-power field). There were marked bile ducts proliferation and a small amount of a yellowish pigment was present in bile canaliculi. In the brain of necropsied cows, there was mild vacuolation (*status spongiosus,* spongy degeneration) observed mainly at the junction of the cerebral grey matter and subcortical white matter of the frontal, parietal and occipital telencephalon, and basal ganglia.

Liver damage characteristic of pyrrolizidine alkaloid poisoning was present in 119 (73,4%) of the 162 biopsied cows. Affected cows were classified in groups according to the severity and morphological aspects observed. Forty-five were classified as mildly affected, i.e, presented only megalocytosis or megalocytosis associated to mild periportal fibrosis. Thirty nine cows were moderately affected; these showed megalocytosis, bile ducts proliferation, and/or moderate periportal to coalescing fibrosis. Thirty-five cows were considered severely affected, i.e, presented megalocytosis associated to marked bile ducts proliferation and diffuse hepatic fibrosis dissecting the hepatocytes cords.

DISCUSSION

Photosensitization is a severe dermatitis of animals resulting from a reaction induced by fluorescent pigments deposited in tissues and exposed to ultraviolet (UV) wave length sunlight (Rowe 1989). This inflammatory reaction is most severe in nonpigmented skin where these reactive compounds are most directly exposed to light in the UV spectrum. Photosensitization is classified into two major types – primary and secondary (Knight & Walter 2001). Primary photosensitization is associated with photodynamic compounds present in certain plants which once absorbed from the digestive tract react in the nonpigmented skin with UV light to cause severe dermatitis. Secondary or hepatogenous photosensitization occurs when the liver fails to remove phylloerythrin, a bacterial breakdown product of chlorophyll that can react with UV light to cause photosensitization (Tokarnia et al. 2012b). In Brazil as in other parts of the world, the hepatogenous type of photosensitization is far more common and severe than the primary photosensitization (Tokarnia et al. 2012b). Main plants that may cause primary photosensitization in livestock in Brazil include *Fagopyrum esculentum*, *Ammi majus,* and *Froehlichia humboldtiana*. The latter two were described in Southern and Northeastern Brazil respectively. *F. esculentum* is a crop from southern Brazil but there is no report of photosensitization in livestock associated with this plant in the country (Tokarnia et al. 2012b). Several plants are associated with hepatogenous photosensitization in livestock in Brazil including *Brachiaria* spp., *Lantana* spp., *Panicum dichotomiphlorum*, *Myoporum laetum,* and *Enterolobium gummiferum* (Tokarnia et al. 2012b). None of these plants were found in the pasture where the outbreak reported here occurred.

The pasture of the farm where this outbreak occurred were highly infested by blooming *Senecio brasiliensis*. In addition, histopathological findings in the liver of biopsied and necropsied cows were characteristic of pyrrolizidine alkaloid poisoning in cattle (Driemeier et al. 1991, Barros et al. 1992). Chronic aflatoxicosis should be consider as a differential diagnosis (Pierezan et al. 2010) but this was ruled out since adult cattle are relatively resistant to aflatoxicosis and did not have access to possible aflatoxin sources. Therefore, it was concluded that *Senecio brasiliensis* poisoning was the culprit in this outbreak.

Additionally to being present in *Senecio* species, pyrrolizidine alkaloids are also found in plants of the following genera: *Crotalaria, Erechtites, Heliotropium, Echium, Trichodesma, Cynoglossum* e *Amsinckia* (Stalker & Hayes 2007, Tokarnia et al. 2012b). These plants when ingested cause progressive and irreversible damage to hepatocytes characterized by mitotic inhibition. Hepatocytes do not divide further, but still synthesize DNA and this causes them to increase in size, i.e, megalocytosis (McLean 1970). Eventually hepatocytes die and fibroplasia and bile ducts proliferation take in (Stalker & Hayes 2007). In terminal phases, hepatocytes do not metabolize urea and hyperammonemia ensues. Hyperamonemia is considered the cause of death in seneciosis (Stalker & Hayes 2007). Ammonia is toxic to the central nervous system causing vacuolation (spongy degeneration) in the white matter (Riet-Correa & Méndez 2007, Stalker & Hayes 2007), as observed cattle of this outbreak. Clinical signs are characteristic of hepatic encephalopathy: apathy or hyperexcitability, incoordination, aggression, tenesmus, diarrhea, and rectal prolapse usually for 24-96 hours (Barros et al. 1987).

Photosensitization related to hepatic damage due seneciosis is not a common finding in cattle (Barros et al. 1987), differently from sheep (Barros et al. 1989, Ilha et al. 2001) and horses (Pilati & Barros 2007). However, there are few reports of *Senecio* poisoning in cattle in which the clinical course was prolonged (20-60 days) and the main clinical sign was photosensitization (Motta et al. 2000, Guagnini et al. 2006) as was the case of the cows from this report. When hepatic damage is multifocal, photosensitization tends to be less likely, because there are enough healthy hepatocytes to remove phylloerythrin from bloodstream (Kellerman et al. 2005). In these cases, the hepatic injury was diffuse with substitution of the hepatic parenchyma by connective tissue. Supplementation with proteinated salt might have increased the ingestion of *S. brasiliensis*, since the administration of protein sources is known to enhance intake and digestibility of low-quality forages (Köster et al. 1996).

Liver function tests showed elevated serum level activity of gamma glutamyl transferase (GGT), which is an induced enzyme. GGT increased serum activity in cholestasis may occur by an increase in enzyme production and solubility of GGT adhered to the cell membrane (Hoffmann & Solter 2008). Serum GGT activity remains high throughout the course of the disease, whereas other enzymes are constantly changing. Consequently, determination of serum GGT activity is the best parameter for biochemical diagnosis of *Senecio* spp. poisoning in cattle (Johnson et al. 1985, Craig et al. 1991).

In conclusion *Senecio* spp. poisoning in cattle should be a differential diagnosis in cases of photosensitivity. Although uncommon, cases of photodermatitis associated with seneciosis have been reported, especially if the clinical course is prolonged and liver damage is diffuse. The diagnosis can be made through the liver biopsy and epidemiological evidences.

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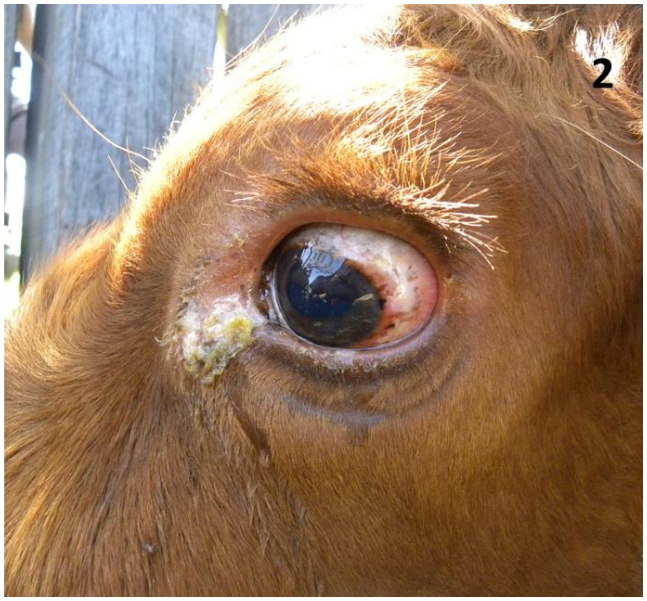
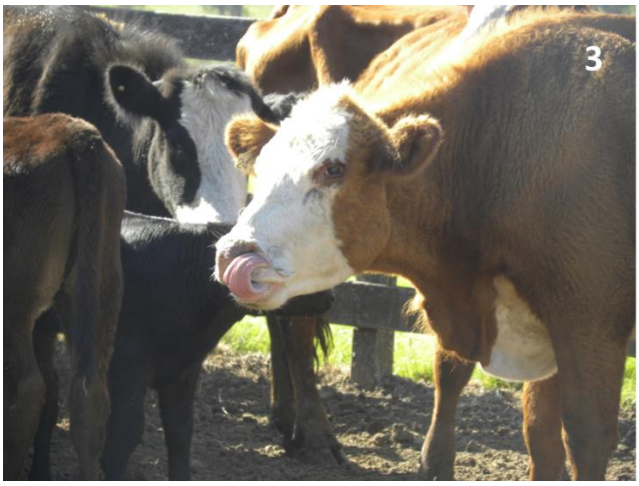


Fig.1. Blooming *Senecio brasiliensis* specimen observed in the pasture where the cattle affected in the outbreak of seneciosis were held.

Fig.2. Cow affected with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis showing conjuntival hyperemia and mucopurulent ocular discharge.



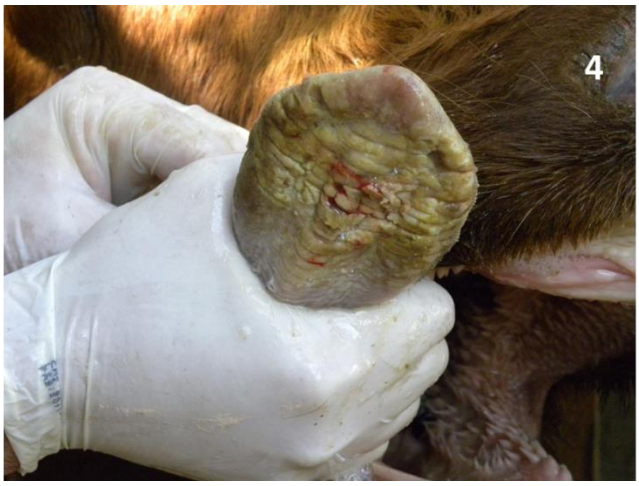
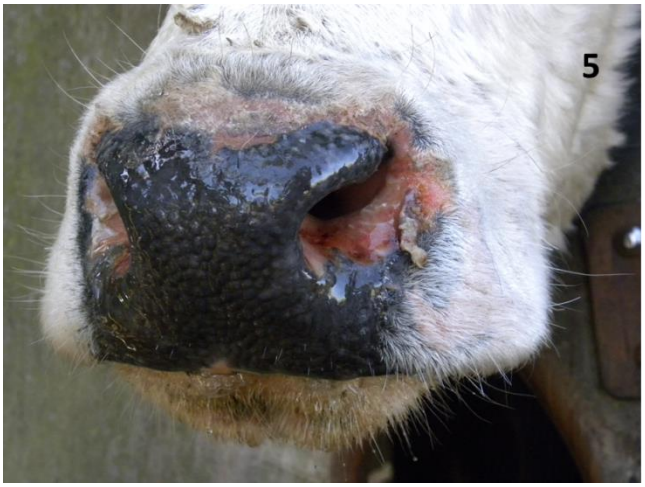


Fig.3. Cow affected with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis showing nasal discharge which provoked a continuous licking of the nose.

Fig.4. Cow affected with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis showing ventral diphteric glossitis caused by persistent exposure of the ventral surface of the tongue to sunlight.



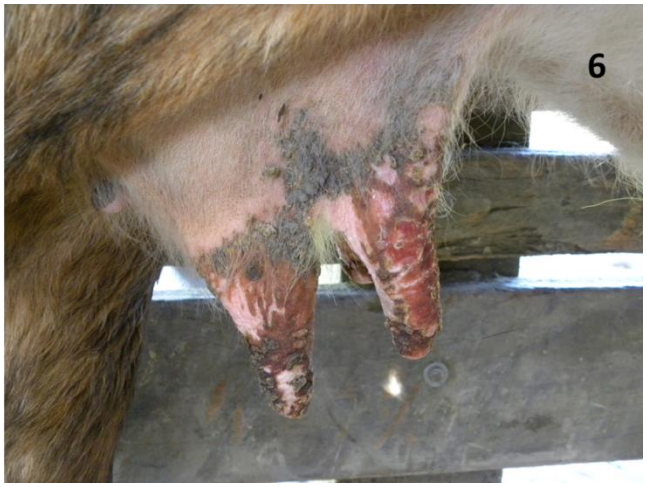
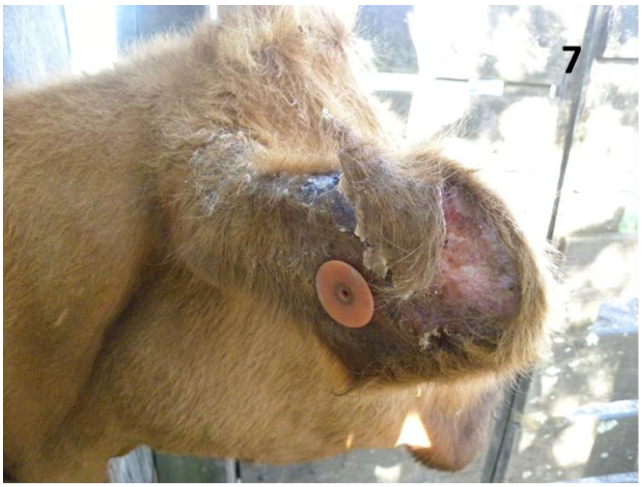


Fig.5. Erosions and ulcerations of the nasal plane covered by crusts in a cow with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis.

Fig.6. Skin of teats and udder showing ulcerations and crusts. Photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis.



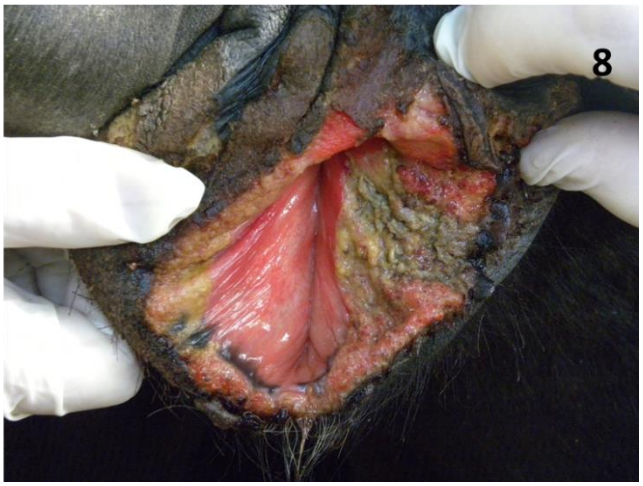
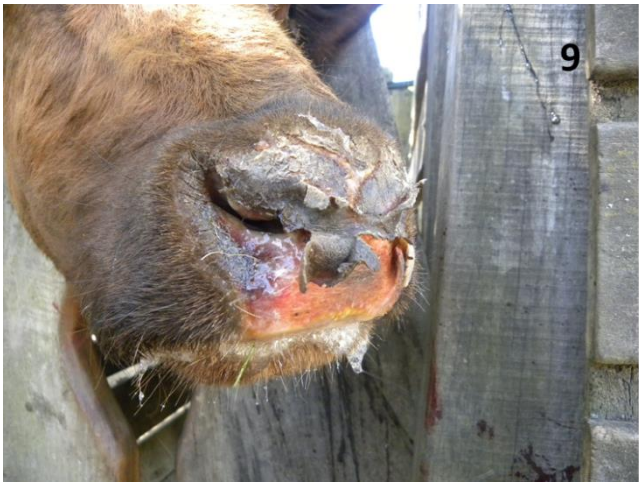


Fig.7. Crusts and ulcers of the skin of the dorsum of ears. Photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis.

Fig.8. Fibrinonecrotizing vulvitis and vestibulitis. Cow with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis.



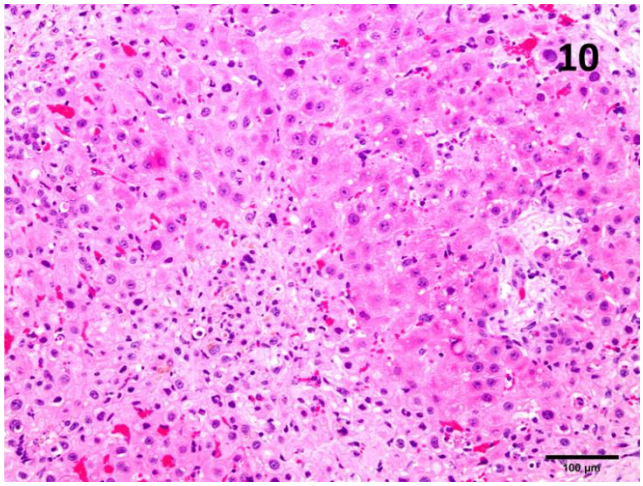


Fig.9. Cow with photosensitivity due to liver failure in *Senecio brasiliensis* toxicosis. Portions of sloughed off necrotic skin imparting to the lesion an aspect of the bark of a tree.

Fig.10. Liver biopsy of an affected cow in the outbreak of seneciosis. Disruption of hepatic architecture. The lobules are dissected by fibrous connective tissue. The remaining hepatocytes form a nodule surrounded by connective tissue. Numerous megalocytes can be observed. HE, obj.20x.

1. ARTIGO 2

Clinical and pathological aspects of chronic *Senecio* spp. poisoning in sheep

Paula R. Giaretta, Welden Panziera, Márcia E. Hammerschmitt, Ronaldo M. Bianchi, Glauco J.N. Galiza, Ingrid S. Wiethan, Talissa Bazzi e Claudio S.L. Barros

2º. TRABALHO

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Clinical and pathological aspects of chronic *Senecio* spp. poisoning in sheep[6]

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ABSTRACT.- Giaretta P.R., Panziera W., Hammerschmitt M.E., Bianchi R.M., Galiza G.J.N., Wiethan, I.S., Bazzi, T. e Barros C.S.L. 2014. **Clinical and pathological aspects of chronic *Senecio* spp. poisoning in sheep.** *Pesquisa Veterinária Brasileira 00(0):000-000.* Departamento de Patologia, Universidade Federal de Santa Maria, Camobi, Santa Maria, RS 97105-900, Brazil. E-mail: claudioslbarros@uol.com.br

This paper describes an outbreak of chronic *Senecio* spp. poisoning in grazing sheep in Rio Grande do Sul, Brazil, causing the death of 10 out of 860 adult sheep. Eight sick ewes were euthanized and necropsied. Cattle from this farm were also affected. Clinical signs included progressive weight loss, apathy, and photosensitization. Four out of seven tested sheep had increased gamma-glutamyl transferase serum activity and two of them presented serum elevation of alkaline phosphatase. At necropsy, three out of eight ewes presented slightly irregular toughened livers with multifocal nodules, two out of eight ewes had a whitish liver with thickened fibrotic Glisson's capsule partially adhered to the diaphragm, and three out of eight ewes had smooth and grossly normal livers. Necropsy findings attributed to liver failure included hydropericardium (7/8), ascites (5/8), icterus (2/8), hydrothorax (1/8), and edema of mesentery (1/8). The main hepatic histological findings that allowed the establishment of the diagnosis were megalocytosis, proliferation of bile ducts, and fibrosis. Spongy degeneration was observed in the brains of all eight necropsied sheep and was more severe at the cerebellar peduncles, pons, and mesencephalon. These are suggested as the portions of election to investigate microscopic lesions of hepatic encephalopathy in sheep with chronic seneciosis. The diagnosis of *Senecio* spp. poisoning was based on epidemiology, clinical signs, laboratory data, necropsy, and histological findings.

INDEX TERMS**:** *Senecio* spp., seneciosis, pyrrolizidine alkaloids, diseases of sheep, pathology, liver, hepatic encephalopathy.

Resumo.-[**Aspectos clínico-patológicos da intoxicação crônica por *Senecio* spp. em ovinos**]. Neste trabalho, relata-se um surto de intoxicação crônica por *Senecio* spp. em ovinos no estado do Rio Grande do Sul, Brasil. Dez ovelhas adultas de um rebanho de 860 ovinos morreram com sinais da doença e oito que estavam doentes foram eutanasiadas e necropsiadas. Na propriedade a doença também foi observada em bovinos. Os sinais clínicos nas ovelhas incluíam emagrecimento, apatia e fotossensibilização. Quatro ovelhas, de um total de sete que foram testadas, apresentaram aumento da atividade sérica da gama glutamil transferase e duas apresentaram fosfatase alcalina sérica elevada. Na necropsia, em três dos oito ovinos necropsiados, o fígado estava levemente mais firme, com superfície capsular ligeiramente irregular e com nódulos pálidos na superfície de corte. Em outros três ovinos o fígado era macroscopicamente normal. Em dois dos oito ovinos necropsiados a cápsula de Glisson era brancacenta devido à fibrose e parcialmente aderida ao diafragma. Adicionalmente, foram observadas alterações macroscópicas atribuíveis à insuficiência hepática como hidropericárdio (7/8), ascite (5/8), icterícia (2/8), hidrotórax (1/8) e edema no mesentério (1/8). Histologicamente, as principais alterações observadas, que contribuíram para o estabelecimento do diagnóstico de intoxicação crônica por alcaloides pirrolizidínicos nas ovelhas deste surto foram hepatomegalocitose, proliferação de ductos biliares e fibrose. Todas as ovelhas apresentavam degeneração esponjosa grave no cerebelo e pedúnculos cerebelares, ponte e mesencéfalo. Sugere-se que esses sejam os sítios anatômicos de eleição no encéfalo para a observação dessa lesão em ovinos com intoxicação por *Senecio* spp. O

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diagnóstico de intoxicação por *Senecio* spp. foi baseado na epidemiologia, achados clínicos, laboratoriais, de necropsia e histopatológicos.

TERMOS DE INDEXAÇAO**:** *Senecio* spp., seneciose, alcaloides pirrolizidínicos, doenças de ovinos, patologia, fígado, encefalopatia hepática.

INTRODUCTION

Senecio spp. are the most common hepatotoxic plants causing chronic poisoning in livestock in Brazil, being especially important in the South (Tokarnia et al. 2002). Poisoning by *Senecio* spp. plants are the most important cause of death in adult cattle in central region of the State of Rio Grande do Sul (Lucena et al. 2010).

Sheep are considered markedly resistant to *Senecio* spp. poisoning either due to peculiarities of their ruminal flora (Craig et al. 1992) or to enzymatic liver complexes (Huan et al. 1998) which result in a remarkable ability to detoxify pyrrolizidine alkaloids contained in these plants. Accordingly, sheep grazing has been generally recommended as a biological control for *Senecio* spp. (Soares et al. 2000, Bandarra et al. 2012, Karam et al. 2013). Studies have indicated that sheep continuously stocked at 0.43 sheep/hectare (Soares et al. 2000) and 3.0 sheep/ha (Bandarra et al. 2012) can control *Senecio* spp. in the field. Although rare, however, outbreaks of *Senecio* spp. poisoning in sheep, have been reported in Brazil (Ilha et al. 2001, Grecco et al. 2011) and the indiscriminate use of sheep to control the plant might not be safe (Dollahite 1972) because sheep held for several years in pastures markedly invaded by *Senecio* spp. may be affected after ingesting large amounts of the weed (Seaman 1985, Seaman & Dixon 1989).

Although the practice of controlling *Senecio* spp. growth by sheep grazing should continue to be encouraged, diagnostic parameters must be established for detecting outbreaks of pyrrolizidine alkaloids poisoning in sheep, allowing for avoiding further losses. The aim of the current study is to report an outbreak of chronic *Senecio* spp. poisoning in sheep and to describe the clinical, gross, and histopathological aspects of the toxicosis. It is concluded that, taken together, the changes described here are diagnostic for the condition.

MATERIAL AND METHODS

The data of this report were obtained in a visit to the farm where the outbreak occurred. During that visit, eight affected sheep were clinically examined and subsequently euthanized and submitted to necropsy, due the severity of clinical presentation. Seven out of the eight affected sheep were bled for liver function tests (aspartate aminotransferase [AST], gamma glutamyl transferase [GGT], alkaline phosphatase [AP]), and complete red cell count. Several tissues were sampled at necropsies and routinely processed for histopathology. Nine cattle of both sexes from the farm where this outbreak occurred were clinically examined and submitted to liver biopsy using a technique previously described (Barros et al. 2007). Liver samples were formalin-fixed and routinely processed for histology.

For the representative analysis of spongy degeneration in different regions of sheep brains, several transversal cuts were performed in a 0,5-1cm interval. For histological evaluation the following transversal sections were systematically collected and processed: (1) Cerebellum and cerebellar peduncles; (2) pons; (3) frontal lobe; (4) parietal lobe; (5) occipital lobe; (6) medulla at the obex; (7) hippocampus; (8) basal nuclei; (9) mesencephalon; and (10) thalamus. Spongy degeneration was evaluated independently by two pathologists and classified as mild, moderate, and severe.

RESULTS

This outbreak occurred in a farm located in Santiago, Rio Grande do Sul, Brazil (29° 10′ 23″South, 54° 51′ 21″West, 354 meters above sea level). Sheep and cattle were placed in a pasture highly infested by *Senecio* spp., where they spent the winter (June to August) of 2013 under a shortage of forage caused by overgrazing. Ten sheep from a herd of 860 died since December 2013 to the end of March 2014 with clinical signs of progressive weight loss, apathy and photosensitization. Eight 2 to 4-year-old ewes were sick at the moment when the farm was visited by the authors in March 21, 2014. About 80 adult cattle from a herd of 1,300 died on this farm in 2013, presenting diarrhea, weight loss, and tenesmus. Some cattle also exhibited aggressiveness and photosensitization.

At clinical examination, ewes were apathetic, markedly thin (Fig.1), and presented slightly pale mucous membranes. All sheep had varying degrees of photodermatitis characterized by crusty lesions in the ears (Fig.2) and nose. Results of liver function tests are shown on Table 1. Red blood tests revealed mild normocytic normochromic anemia. At necropsy, three out of eight ewes presented a slightly irregular toughened liver (Fig.3 and 4). There were multifocal tan 2-5mm in diameter nodules (Fig.5). In two out of the eight necropsied ewes the liver was whitish due to thickening of Glisson's capsule by fibrosis and portions of the parietal liver capsule were adhered to the diaphragm (Fig.6). No gross lesions could be detected in three out of the eight necropsied ewes. All the necropsied sheep had a distended gall bladder and mild abomasal infection by *Haemonchus contortus*. Other necropsy findings included hydropericardium (7/8), ascites (5/8), icterus (2/8), hydrothorax (1/8), and mesenteric edema (1/8).

Varying degrees of microscopic changes attributed to alkaloid pyrrolizidine toxicosis were observed in the liver of all eight necropsied ewes; these included fibrosis which ranged from periportal to dissecting some hepatocytes cords (Fig.7 and 8). Fibrosis was milder in the livers that were grossly normal. There was biliary duct hyperplasia in the portal triads (Fig.8) and Kupfer cells were hypertrophic. Hepatocytes were enlarged in size, with abundant cytoplasm and large nuclei (Fig.9). Several nuclei had a single vacuole, displacing the nuclear chromatin to the periphery and giving an empty aspect to the nuclei. Numerous hepatocytes contained an oval, intranuclear, and eosinophilic inclusion (Fig.10). A variable number of macrophages with brown and granular pigment interpreted as copper and lipofuscin in the cytoplasm was present (Fig.11). Nodules were not visible histologically.

Histological findings in the brain consisted of large empty spaces in the white matter in the brainstem, cerebellum, thalamus, basal nuclei and in the junction of the white and grey matter in the cerebrum (Fig.12). Distribution and severity of spongy degeneration in different cuts of the brains are shown on Table 2.

Affected cattle submitted for clinical examination and liver biopsy on the day of the visit to the farm were in poor body condition and one of them presented edema in the submandibular region. Seven from nine biopsied cattle had typical hepatic histological lesions of pyrrolizidine alkaloids poisoning. There was disruption of hepatic architecture, where the cords and lobules were dissected by abundant connective tissue and fibrosis. There was marked hepatocellular megalocytosis and severe bile duct hyperplasia.

DISCUSSION

The clinical, epidemiological, gross and histopathological findings in sheep from this outbreak are similar to those previously described for chronic pyrrolizidine alkaloid (PA) poisoning in sheep (Ilha et al. 2001, Grecco et al. 2011). Sheep are believed to be relatively resistant to PA action due to ruminal detoxification (Craig et al. 1992) or to the low rates of pyrrole metabolite production coupled with high concentration of hepatic detoxifying enzymes system and efficient glutathione conjugation (Huan et al. 1998).

Although sheep grazing is considered efficient to control *Senecio* at pasture, if they are kept for several years under conditions of shortage of forage and in areas highly infested by plants containing pyrrolizidine alkaloids, they can get sick (Seaman 1985, Seaman & Dixon 1989). The plants most often implicated with alkaloid pyrrolizidine toxicosis in sheep are *Heliotropium europaeum* and *Echium plantagineum* (Stalker & Hayes 2007). In some regions of Australia, *Echium plantagineum* and *Heliotropium europaeum* poisoning is considered the main cause of death in sheep due to plant poisoning (St George-Grambauer & Rac 1962, Seaman 1985, 1987). There are reports of *Jacobaea maritima* (formerly *Senecio cineraria*) poisoning in sheep in Iraq (Forsyth 1979), *S. madagascariensis* in Australia (Seaman 1987), and *S. sanguisorbae* in Mexico (Rosiles & Paasch 1982). Clinical signs may not be seen until after a second season of exposure (Stalker & Hayes 2007). Probably, poor management practices have resulted in the outbreak of seneciosis in sheep reported here, since cattle were also affected in the same farm.

Two different clinicopathological syndromes can affect sheep grazing plants containing pyrrolizidine alkaloids: (1) pyrrolizidine proper alkaloids poisoning (Seaman 1987) and (2) chronic copper poisoning secondary to pyrrolizidine alkaloids poisoning or hepatogenous chronic copper poisoning (Bull et al. 1956, St George-Grambauer & Rac 1962, Seaman 1987). The chronic damage to hepatocytes results in an enhanced uptake and accumulation of copper in the liver (Bull et al 1956) that under certain conditions can be released from the liver to the blood stream causing intravascular hemolysis (Stalker & Hayes 2007). Hepatogenous chronic copper poisoning was not observed in sheep from the outbreak reported here, probably because sheep were euthanized or due to the fact they were not receiving copper-containing supplements. It is suggested that the occurrence of hepatogenous chronic copper poisoning associated with PA poisoning in sheep is related to an additional source of copper (Howell et al. 1991, Ilha et al. 2001).

The gross presentation of the livers from sheep with *Senecio* spp. poisoning was variable, consisting either of a multinodular aspect and thickened white capsule aspect, which is comparable with previous descriptions of *Senecio* spp. poisoning in sheep (Ilha et al. 2001, Grecco et al. 2011). It was noticed that the consistency of these livers was less firm than what is usually observed in cases of this condition in cattle. This difference is attributed to variable propensity to fibroplasia within species and to the degree of exposure; fibroplasia usually is minimal in sheep, moderate in horses and marked in cattle (Stalker & Hayes 2007). Two sheep from this outbreak had grossly normal livers, although histological findings were characteristic of pyrrolizidine alkaloid poisoning. It is believed that these two cases represent an early stage of the disease.

The main histological findings in the liver that allowed the establishment of the diagnosis were hepatocellular polyploidy known as megalocytosis, proliferation of bile ducts epithelial cells in the portal triads, and periportal fibroplasia (Stalker & Hayes 2007). Other histological features in the liver that additionally add in the diagnosis were the intranuclear inclusions and hepatocytes with empty nuclei.

Megalocytosis is the hallmark of PA toxicosis (Bull et al. 1969) and occurs as a consequence of pyrrolizidine alkaloid action, inhibiting DNA synthesis and mitosis in hepatocytes. However, some hepatocytes are able to produce DNA without mitosis, resulting in enlarged hepatocytes with large polyploid nuclei (Stalker & Hayes 2007). Affected hepatocytes die and are replaced by cholangiolar epithelia that proliferate in response to regenerative stimuli when liver mass is inadequate (Stalker & Hayes 2007). Hepatic fibrosis is evident in all animal species with chronic seneciosis (Kellerman et al. 2005) and it is initially seen in the portal tract (Walker & Kirkland 1981, Torres & Coelho 2008).

Intranuclear inclusions in pyrrolizidine alkaloid poisoning correspond to part of the cytoplasm that is sometimes invaginated by the enlarged nuclei (Kellerman et al. 2005, Stalker & Hayes 2007). Hepatocytes described as having a single nuclear vacuole displacing the nuclear chromatin (empty nuclei) were similar to those seen in great number in human beings with Wilson disease, diabetes mellitus, prolonged congestive heart failure, and some other disorders (Geller & Petrovic 2009). These 'glycogen nuclei" or glycogenated nuclei are present in small numbers in humans with no recognizable disease. The normal hepatocyte also contains abundant glycogen which is not seen with hematoxylin-eosin but is easily demonstrated with the PAS reaction (Geller & Petrovic 2009).

Spongy degeneration was observed in all the brains and was more severe in cerebellar peduncles, mesencephalon, thalamus, and pons, according to previous descriptions in sheep (Hooper 1975, Ilha et al. 2001, Kellerman et al. 2005) and cattle (Wouters et al. 2013). Apparently, no neurological signs were observed in any of the sheep as also recognized elsewhere (Kellerman et al. 2005). This can also be associated with the fact that sheep were euthanized and the whole clinical course was not observed, but the most probable explanation is that very often neurological disease manifested by sheep with brain lesions are not conspicuous and manifest solely as apathy.

Morphological changes in hepatic encephalopathy in the central nervous system of human beings and horses centers on astrocytes (Harris et al. 2008, Crawford 2005). Astrocytes undergo Alzheimer type II change in which they show enlarged pale nuclei with a rim of chromatin and prominent nucleoli. Astrocytes pairs and triplets are seen, and in severe cases nuclei may become lobulated and may contain glycogen (Stalker & Hayes 2007, Harris et al. 2008). Cirrhosis of the liver results in elevated ammonia levels in blood and brain and it is the ammonia toxicity that is the leading hypothesis for the causation of hepatic encephalopathy (Harris et al. 2008). An astrocytic phenotype similar to Alzheimer type II change can be induced by hyperammonemia in experimental animals and tissue culture and is also seen in human patients with congenital hyperammonemia due to inherited disorders involved in the urea cycle (Butterworth 1993). Morphological findings in ruminants with hepatic encephalopathy are characterized by microcavitation of the white matter in the brain named *status spongiosus* or spongy degeneration (Finn & Tennant 1974, Barros 2010). The spongy change is due to intramyelinic edema, causing splitting and vacuolation of myelin sheaths (Zachary 2012).

Serum liver enzyme activities were variable in these sheep. Four out seven tested sheep had increase in GGT serum activity and two out of seven sheep presented increased serum activity of AP. Enzymatic elevation were not proportional to liver injury observed. It is known that serum enzyme changes precede development of recognizable histologic lesions in the liver of calves with chronic seneciosis and serum glutamate dehydrogenase is the first enzyme to increase in most animals (Craig et al. 1991). This enzyme change is followed by increases in alkaline phosphatase and gamma-glutamyl transferase (Craig et al. 1991). It is concluded that elevations of GGT activities could be used to predict the onset of clinical illness in sheep. Findings of normocytic normochromic anemia in red blood tests of sheep from the current outbreak were attributed to *Haemonchus contortus* infection (Abott et al. 1984).

In conclusion, histological changes are the most important features for the diagnosis of *Senecio* spp. poisoning in sheep and differential diagnosis must be made with poisoning by other plants that contains pyrrolizidine alkaloids.

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Table 1. Results of biochemical tests compared with the severity of liver lesions observed in seven sheep poisoned by *Senecio* spp. [a]

Sheep	Hepatic lesion	AP[b] (68-387 U/L)[c]	AST[d] (20-280 U/L)	GGT[e] (20-52 U/L)
2	+	159	82	68
3	++	228	94	43
4	+	167	176	92
5	+++	157	146	21
6	+	1178	77	111
7	+	210	77	35
8	+	1216	100	58

[a]+++severe; ++moderate; +mild; [b]alkaline phosphatase; [c]unit per liter (reference values from Hoffmann & Solter 2008); [d]aspartate aminotransferase; [e]gamma glutamyl transferase,

Table 2. Distribution and severity of spongy degeneration in the brain of sheep with chronic poisoning by *Senecio* spp. compared to the severity of hepatic lesions[a]

Sheep	Hepatic lesion	Cerebellum and cerebellar peduncle	Pons	Frontal lobe	Parietal lobe	Occipital lobe	Brainstem	Hypocampus	Basal nuclei	Mesencephalon	Thalamus
1	+	+++	+++	++	+	NC[b]	++	NC	++	+++	+++
2	+	+++	+++	++	++	+	++	NC	+	+++	++
3	++	+++	+++	++	++	NC	NC	NC	++	+++	++
4	+	+++	+++	++	+	NC	NC	NC	+++	+++	+++
5	+++	+++	+++	+	+	NC	+++	NC	+++	+++	+++
6	+	+++	+++	++	+	NC	+++	NC	++	+++	+++
7	+	+++	+++	++	+	NC	++	NC	++	+++	+
8	+	+++	+++	++	++	+	++	NC	++	+++	+++

[a]+++severe; ++moderate; +mild lesion;[b] no changes.

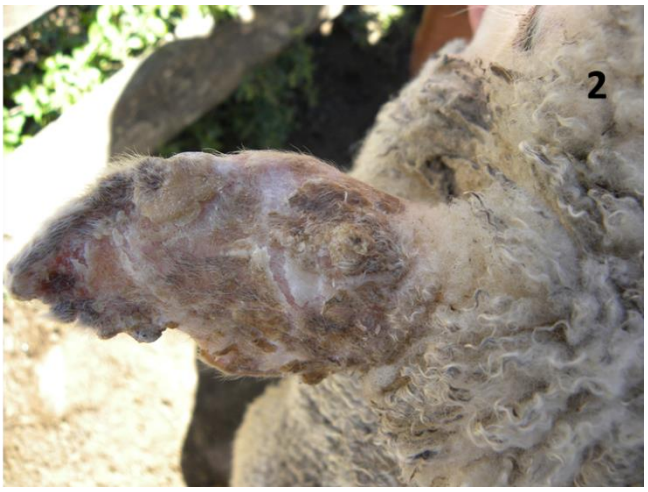
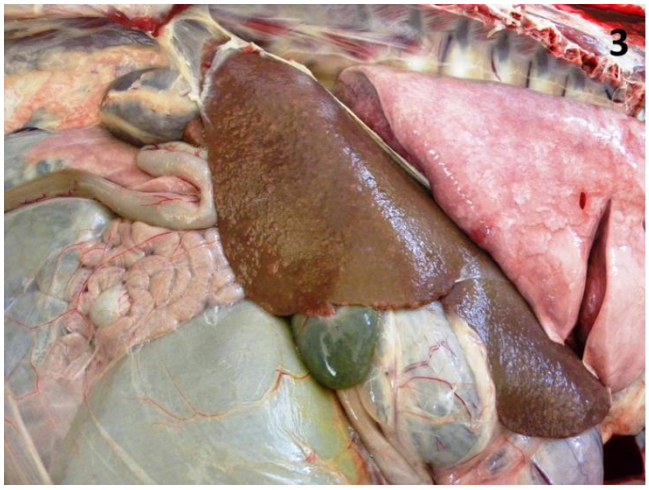


Fig.1. Sheep with poor body condition due to liver failure in *Senecio* spp. toxicosis.

Fig.2. Crusts of the skin of the dorsum of ears. Photosensitivity in sheep due to liver failure in *Senecio* spp. toxicosis.



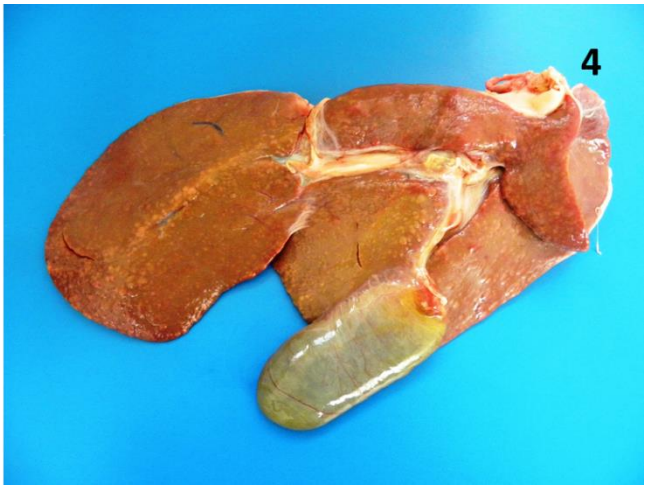


Fig.3. Liver with an irregular capsular surface in sheep with *Senecio* spp. toxicosis.

Fig.4. Visceral surface of the liver with multifocal to coalescing nodules and distended gall bladder in sheep with *Senecio* spp. toxicosis.

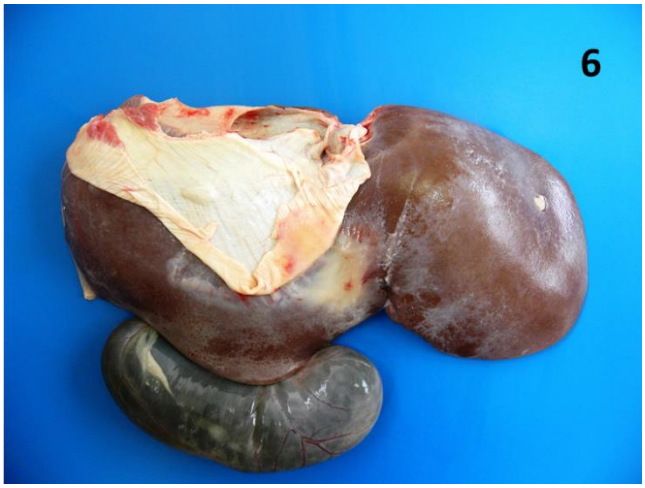
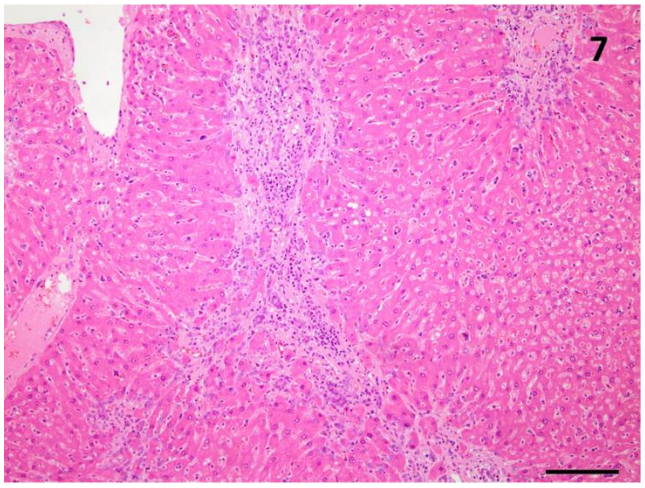


Fig.5. Cut surface of the liver showing multifocal tan nodules that range from 2-5 mm in diameter. Sheep with *Senecio* spp. toxicosis.

Fig.6. Liver of sheep affected by *Senecio* spp. toxicosis. Parietal surface of the liver showing whitish areas of fibrosis attached to the diaphragm. The gall bladder is markedly distended.



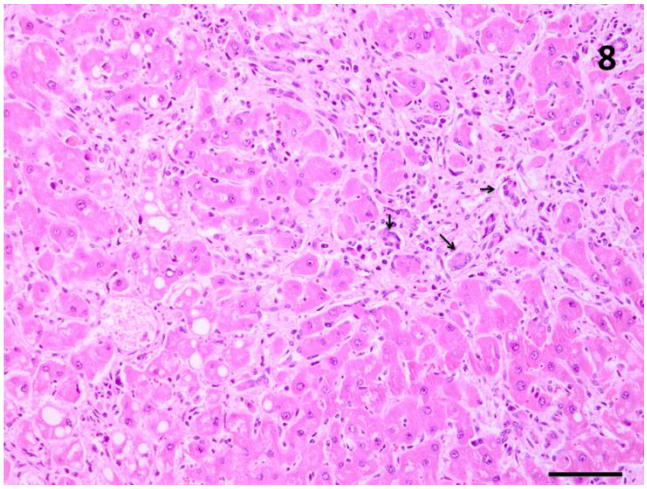


Fig.7. Histology of the liver of a sheep affected by *Senecio* spp. toxicosis. Portal tract is distended by fibrous connective tissue and biliary duct proliferation. HE, obj.10x.

Fig.8. Histology of the liver of a sheep affected by *Senecio* spp. toxicosis. Cords of hepatocytes are dissected by connective tissue and there is marked hyperplasia of biliary ducts (arrows). HE, obj. 20x.

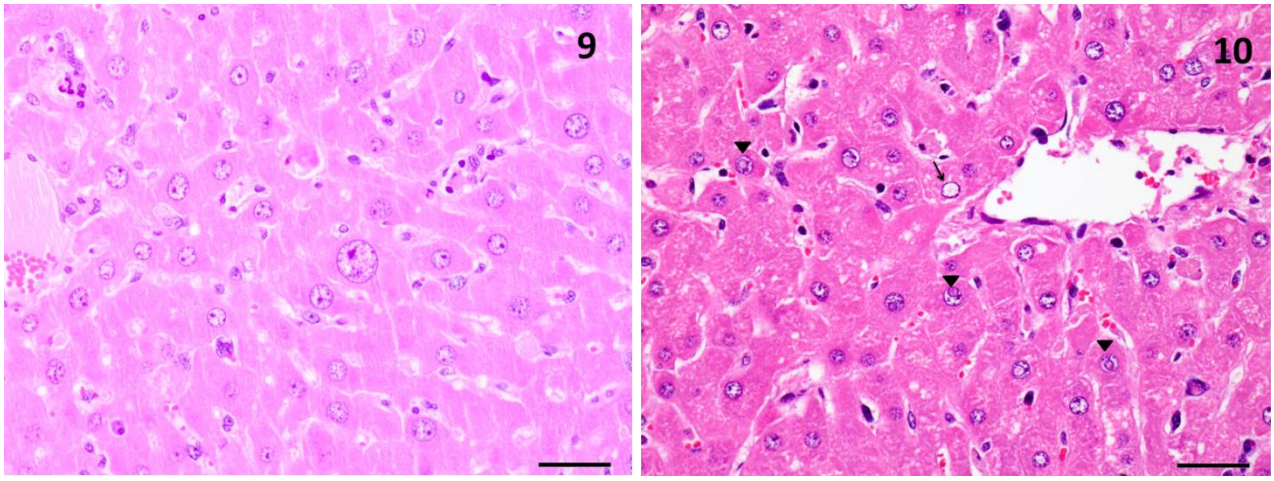


Fig.9. Histology of the liver of a sheep affected by *Senecio* spp. toxicosis. Hepatocyte with an enlarged nucleus (megalocyte). HE, obj.40X.

Fig.10. Histology of the liver of a sheep affected by *Senecio* spp. toxicosis. Nucleus of a hepatocyte (arrow) with a single vacuole displacing the nuclear chromatin to the periphery (empty nucleus). Numerous hepatocytes contained an oval, intranuclear, and eosinophilic inclusion (arrowheads). HE, obj.40x.

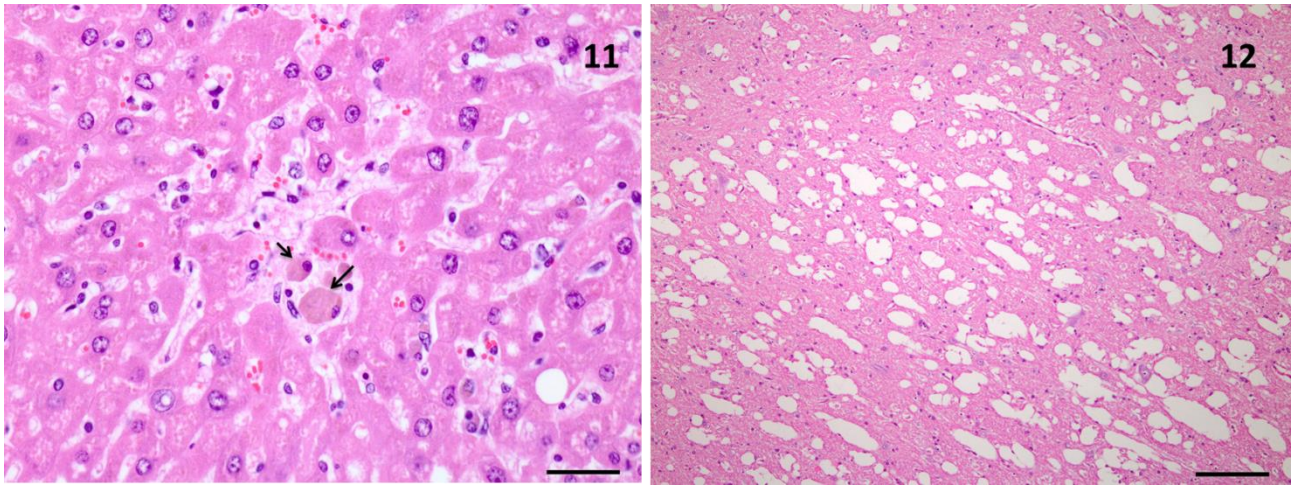


Fig.11. Histology of the liver of a sheep affected by *Senecio* spp. toxicosis. Macrophages with brown and granular pigment in the cytoplasm interpreted as copper and lipofuscin (arrows). HE, obj.40x.

Fig.12. Histology of the brain (thalamus) of a sheep affected by *Senecio* spp. toxicosis. Severe spongy degeneration in the white matter. HE, obj.10x.

2. DISCUSSÃO

Nesta dissertação são incluídos dois artigos científicos referentes às descrições de dois surtos de intoxicação espontânea por *Senecio* spp. em ruminantes: um em bovinos e outro em ovinos.

O primeiro artigo é resultado de visitas periódicas realizadas durante o ano de 2013 e 2014 a propriedades de bovinocultura de corte extensiva no Rio Grande do Sul, onde havia a suspeita de intoxicação por *Senecio* spp. Durante este período, foram visitadas 17 propriedades nos municípios de Santa Maria, Dilermando de Aguiar, São Sepé, Cachoeira do Sul, São Vicente do Sul, Santiago, Cacequi e Alegrete, onde biópsias hepáticas foram realizadas em mais de 900 bovinos, a fim de estabelecer-se o diagnóstico da intoxicação por *Senecio* spp. O primeiro artigo foi elaborado com o objetivo de descrever um surto de seneciose em bovinos, onde a fotossensibilização foi o principal sinal clínico observado e com uma alta prevalência, sendo que estas lesões não são comumente relacionadas com esta intoxicação nesta espécie. Neste surto, 119 vacas de um rebanho de 162 foram acometidas, sendo que 83 delas apresentaram sinais clínicos de fotodermatite. Os principais sinais clínicos observados foram emagrecimento, lacrimejamento excessivo ou secreção ocular mucopurulenta, secreção nasal serosa, glossite diftérica ventral e crostas no plano nasal, tetos, ponta das orelhas e na vulva. Três vacas foram necropsiadas e o fígado era firme, a vesícula biliar estava distendida e havia edema no mesentério e no abomaso. Todas as vacas do rebanho foram biopsiadas e os principais achados histopatológicos dos 119 bovinos considerados acometidos pela intoxicação foram fibrose hepática, megalocitose e proliferação de ductos biliares. Seis vacas testadas apresentaram aumento da atividade sérica da gama glutamil transferase. As lesões histológicas nos fígados dos bovinos necropsiados eram semelhantes às dos fígados biopsiados e observou-se espongiose no encéfalo das vacas necropsiadas. A alta prevalência de fotossensibilização nos bovinos deste surto foi atribuída ao curso clínico prolongado.

O segundo artigo científico foi elaborado com o intuito de descrever um surto de intoxicação por *Senecio* spp. em ovinos em Santiago, Rio Grande do Sul, uma vez que a ocorrência desta condição nesta espécie é incomum. Neste artigo, relataram-se os achados clínicos, laboratoriais, macro e microscópicos da

intoxicação por *Senecio* spp. em oito ovinos. Clinicamente, os ovinos apresentavam emagrecimento e fotodermatite. Macroscopicamente, o fígado de três dos oito ovinos necropsiados estava levemente mais firme, com superfície capsular ligeiramente irregular e com nódulos pálidos na superfície de corte. Em outros três ovinos o fígado era macroscopicamente normal. Em dois dos oito ovinos necropsiados, a cápsula de Glisson era brancacenta devido à fibrose e parcialmente aderida ao diafragma. Os principais achados histopatológicos no fígado de todos os ovinos necropsiados foram megalocitose dos hepatócitos, proliferação do epitélio biliar nas tríades portais, fibroplasia periportal, hepatócitos com núcleos de aspecto vazio ou contendo pseudoinclusões. Espongiose foi observada microscopicamente nos encéfalos de todos os ovinos necropsiados, sendo mais acentuada na região do cerebelo e pedúnculos cerebelares, ponte, mesencéfalo e tálamo. Nos exames bioquímicos, quatro de sete ovinos testados apresentaram aumento da atividade sérica da gama glutamil transferase e dois apresentaram aumento da fosfatase alcalina sérica. O diagnóstico de intoxicação por *Senecio* spp. deste surto foi baseado nos achados clínicos, patológicos e epidemiológicos.

CONCLUSÕES

1. A biópsia hepática é o melhor método para o diagnóstico da intoxicação por plantas do gênero *Senecio* em bovinos.

2. A intoxicação por *Senecio* spp. deve entrar no diagnóstico diferencial em casos de fotossensibilização em bovinos.

3. A elevação sérica da atividade da enzima gama glutamil transferase, embora não seja consistente e específica, pode ser utilizada para auxiliar no diagnóstico da intoxicação por *Senecio* spp. em bovinos e ovinos.

4. Ovinos que apresentam o fígado com aparência macroscópica normal podem ter lesões histológicas e sinais clínicos de intoxicação por alcaloides pirrolizidínicos.

5. Os locais preferenciais para avaliação histológica das lesões de encefalopatia hepática em ovinos intoxicados por *Senecio* spp. são: cerebelo e pedúnculos cerebelares, ponte e mesencéfalo.

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