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The pathology of selected diseases caused by toxic plants in cattle

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Abstract

In Brazil, there are at least 131 described toxic plants belonging to 79 genera. Annual livestock losses due to plant poisoning-associated deaths are estimated to range from 820,761 to 1,755,763 cattle, 399,800 to 445,309 sheep, 52,675 to 63,292 goats and 38,559 horses. In veterinary diagnostic laboratories around the country, approximately 15% of necropsy diagnoses involve plant poisoning, and in the deep south of the country, the main cause of death in cattle is poisoning by *Senecio* species. Due to time restrictions, we will address cattle intoxication considering only five plants, namely, *Senecio* spp. (ragwort), *Pteridium arachnoideum* (bracken fern), *Ateleia glazioviana*, *Senna occidentalis* (coffee senna), and *Vicia villosa* (hairy vetch). The criteria for the inclusion of these five plants were their abundance and therefore their importance as a cause of death in cattle, the unusual lesions they produce, and general interest since four of them occur in several other countries. In a retrospective study of 16 years of data collected in our veterinary pathology laboratory in southern Brazil, among 2,912 bovine deaths, 461 (15.83%) were due to poisonous plant ingestion, and the 5 plants mentioned above were responsible for more than 80% of these 461 deaths. Ragwort produces overwhelming liver fibrosis, with the expected multiple consequences of liver failure. Bracken ferns are responsible for acute hemorrhagic disease, chronic hematuria and squamous cell carcinomas in the upper alimentary tract. *A. glazioviana* causes cardiac failure, abortion, and intramyelinic edema. Coffee senna induces marked degenerative myopathy. Hairy vetch is associated with systemic granulomatous inflammation. In this presentation, we will discuss the diseases caused by these five plants.

In Brazil, there are at least 131 described toxic plants belonging to 79 genera. Annual livestock losses due to plant poisoning-associated deaths are estimated to range from 820,761 to 1,755,763 cattle, 399,800 to 445,309 sheep, 52,675 to 63,292 goats and 38,559 horses (Riet-Correa et al. 2017).

In this presentation, we have included only the most important diseases caused by plant poisoning in cattle diagnosed at the Veterinary Pathology Laboratory (LPV) of the Federal University of Santa Maria (UFSM), Rio Grande do Sul (RS), Brazil, during the last 16 years (Rissi et al. 2007b). Retrospective surveys showed that 15% of cattle deaths were due to toxic plant-associated diagnoses according to necropsies carried out at the LPV during this period (Rissi et al. 2007a, 2007b, Lucena et al. 2010, Tessele et al. 2012).

These notes are intended to accompany and facilitate an understanding of the slide presentation. When appropriate, the slides presented in the seminar will be cited in the text. The slides are identified as S1, S2, S3 and so forth.

In this presentation, we will address cattle intoxications by five plants, namely, *Senecio* spp., *Pteridium arachnoideum*, *Ateleia glazioviana*, *Senna occidentalis*, and *Vicia villosa* (Table 1)

Plants that cause systemic granulomatous inflammation

Vicia villosa (colloquial name: hairy vetch)

Epidemiology

In Brazil, episodes of poisoning by *Vicia villosa* occur in the south (S10). *V. Villosa* and *V. sativa* are grown in southern Brazil as winter forage, as they have high nutritional value. Poisoning occurs in Holstein and Angus cattle, and adult cattle are more susceptible than young stock. Despite the strong dependence on *Vicia* spp. as forage in some regions of southern Brazil, poisoning is rare. Little is known about the conditions that lead to poisoning. The morbidity rate is 1%-70%, and the case fatality rate is 50%-100% (Barros et al. 2001, Fighera & Barros 2004).

Clinical signs and pathology

Cattle may experience a loss of appetite, pruritus (S6), decreased milk yield, fever, and weight loss. The skin turns thick and corrugated (S5), with loss of elasticity. Continuous eye and nasal discharges occur, causing the animals to constantly lick their noses. Elevated alopecic papules and plaques with a diameter of approximately 5 mm can be seen in both pigmented and unpigmented skin. Occasionally, the lesions coalesce, forming large plaques. As a consequence of scratching to soothe the pruritus, some of these lesions ulcerate (S5). Injuries to the head, neck, and escutcheon are most common. Cough, diarrhea, and conjunctivitis can also occur. Leukocytosis

with monocytosis and eosinophilia can be observed. The length of clinical manifestations may vary from five days to five weeks (Barros et al. 2001, Fighera & Barros 2004).

At necropsy, slightly raised, coalescent, pale, gray, multifocal nodules of different sizes can be seen in various organs, including the heart (S8), lung, spleen, kidney (S2, S7), and adrenal glands. The affected organs are frequently enlarged. The liver may be slightly enlarged with a marked lobular pattern. Histologically, the gross pale nodules reveal to be multiple foci of granulomatous inflammation with varying proportions of epithelioid macrophages, lymphocytes, plasma cells, multinucleated giant cells, and eosinophils (S3 and S9). Skin lesions comprise mild to moderate orthokeratotic hyperkeratosis, with mononuclear infiltration and mild perivascular eosinophilic infiltration (Fighera et al. 2005). Granulomatous lesions can also be seen in the urinary bladder, mammary gland, intestines, ovary, lung, and central nervous system (Barros et al. 2001, Fighera & Barros 2004, Rech et al. 2004).

Toxic principle

The active substance is unknown. A hypersensitivity reaction is suspected. A 7-year-old cow fed 100 kg of *V. villosa* developed the toxicosis. This was the only occasion in which the reproduction of toxicosis was achieved. The cow had recovered from a bout of vetch toxicosis in the previous year (Panciera et al. 1992).

Diagnosis

Diagnosis is based on clinical signs, lesions, and a history of grazing on vetch.

Plants that cause chronic liver damage

Senecio spp. (colloquial names: ragwort, groundsel, stinky Willie)

Epidemiology

In the state of RS, southern Brazil, *Senecio* spp. is responsible for more than 50% of deaths caused by toxic plants in cattle (S13) and approximately 7% of all livestock deaths (Panziera et al. 2018).

Most likely, cattle ingest *Senecio* spp. during late autumn and winter when there is a shortage of forage; in May through August, when the plants are sprouting, the plants have higher concentrations of toxic principles. The majority of clinical cases are observed in spring and winter (Barros et al. 1992), but occasional outbreaks occur throughout the year (Barros et al. 1992). This is related to the potentially long delay between ingestion

and the appearance of clinical signs. Poisoning can also occur from ingesting the plant via contaminated hay or silage (Barros et al. 2007).

Sheep are quite resistant to intoxication by *Senecio* spp. and are used to control these plants in the pasture (Barros et al. 1989). However, outbreaks of *Senecio* poisoning have been reported in sheep moved to pastures severely infested with *Senecio* spp. (Giaretta et al. 2014).

Horses are rarely affected, and few outbreaks have been documented in southern Brazil (Gava & Barros 1997, Panziera et al. 2017).

Clinical signs and pathology

The clinical signs in cattle are variable and are summarized in Table 2. The necropsy and histopathological findings are shown in Table 3.

Toxic principle

The toxic compounds of *Senecio* spp. are pyrrolizidine alkaloids (PAs), which are alkylating agents that cause megalocytosis. Megalocytosis is a term coined in the mid-1950s (Bull 1955) to indicate increases in the volumes of the nuclei and cytoplasm of hepatocytes and, to a lesser extent, other cell types associated with PA poisoning. Megalocytosis is probably due to an antimitotic effect coupled with continuous DNA synthesis, while hepatocytes attempt to replace those that have died. The death of hepatocytes is followed by fibroplasia and the proliferation of cells in the bile ducts. Liver failure can cause icterus, photosensitization, edema, and hepatic encephalopathy. The animal usually dies due to hyperammonemia.

Diagnosis

A presumptive diagnosis is based on the epidemiology, clinical signs and gross lesions and is confirmed by characteristic histological lesions in the liver.

The time between ingestion and the appearance of clinical signs should be considered since death can occur weeks or months after exposure to the plant. The determination of liver enzymes is of little value since they are not specific. Liver biopsies (Barros et al. 2007) are diagnostic.

Radiomimetic plants

Pteridium arachnoideum (Colloquial name: Bracken fern)

A radiomimetic plant is one that imitates the effects of radiation, which is the case in bracken fern, which induces aplasia in the bone marrow and neoplasia in the urinary bladder and digestive system in cattle.

Epidemiology

In Brazil, two species of *Pteridium* (fern) are documented: *P. caudatum* and *P. arachnoideum*, which were previously considered varieties of *P. aquilinum* (Faccin et al. 2017). The plant has a cosmopolitan distribution and grows in sandy and acidic soil. Cattle ingest bracken ferns when they are hungry due to forage shortage and drought, under overgrazing conditions, and when *P. arachnoideum* is burned or cut and resprouts. The entire plant is toxic, but new shoots are the most toxic. There are indications that animals develop an addiction, particularly to young shoots, and after the first experience of ingestion, they continue to search out *P. arachnoideum*. The plant maintains its toxicity after drying. Ingestion of *P. arachnoideum* causes three forms of toxicosis (S25): (i) acute hemorrhagic disease (Anjos et al. 2008, 2009); (ii) chronic enzootic hematuria (Gabriel et al. 2009), and (iii) squamous cell carcinoma (SCC) in the upper digestive tract (Souto et al. 2006, Masuda et al. 2011).

Clinical signs and pathology

Acute hemorrhagic disease.

Acute intoxication occurs when cattle consume approximately 10 g/kg/bw for approximately 10-12 weeks (S26). It affects cattle younger than two years. Morbidity can reach 70%, and case fatality is approximately 100%. The clinical signs result from toxin-induced bone marrow aplasia. The clinical course usually lasts for 3-10 days and manifests as a coarse hair coat, weight loss, a wobbly gait, bloody diarrhea, loss of appetite and high fever (109°F). Bone marrow aplasia leads to thrombocytopenia and neutropenia, which eventually lead to fatal generalized bleeding and secondary infection (S26).

Hemorrhages can be seen in the nose (S27), gums (S28), and digestive tract (S29). The mucous membranes are pale with petechiae on the conjunctiva, gums, and vagina. Sick cattle may remain recumbent for long periods and experience persistent bleeding from injection sites (S29) and insect bites. Milk cows may present with blood in the milk. The blood count indicates marked anemia, neutropenia, and thrombocytopenia (Barros et al. 1987, Anjos et al. 2008, 2009). In general, death occurs one to two weeks after the onset of clinical signs. The clinical course is approximately 3-10 days but can last for a few weeks. At necropsy, the mucous membranes are pale, and there are petechiae, mainly in the gums, conjunctiva, and vagina; and petechiae, ecchymosis and hematomas in the serosae of the thoracic cavity and abdominal viscera (S30). Multifocal areas of

necrosis associated with clusters of bacteria occasionally appear in the liver (similar to those of bacillary hemoglobinuria – S30) and the myocardium. They are attributed to sepsis due to neutropenia. In the intestines, the contents may have a large amount of partially clotted blood, and there may be ulcerations in the intestinal lining. Bone marrow aplasia can be better visualized in histological sections of the sternebrae (S31).

Enzootic hematuria

Enzootic hematuria is a chronic form of bracken fern poisoning that affects mainly dairy cows and draft oxen older than 4. The morbidity rate of enzootic hematuria can reach 10%, and the case fatality rate is 100%.

The main clinical sign is hematuria (S32), which can be intermittent or persistent. Other clinical signs are weight loss, pale mucous membranes, and a decrease in milk production in lactating cows. The clinical course can persist for a length of time – up to a year – eventually followed by death. At necropsy, in addition to poor body condition, a notable finding is the overall paleness of all the viscera. The urine appears red and sometimes contains blood clots. The epithelium of the urinary bladder is thickened, and varying numbers of small bruises or nodules (S33) can be seen in the mucosa. Sometimes well-developed bulky tumors occupy the lumen of the bladder. Histologically, the urinary bladder shows, in addition to various types of non-neoplastic lesions (usually different types of cystitis), various types of neoplasms, such as papillomas, adenomas, adenocarcinomas, carcinomas, fibromas, hemangiomas, hemangiosarcomas, and others. Hematuria due to this disease results from one of these lesions (neoplastic or otherwise) in the urinary bladder eroding/ulcerating and bleeding.

SCCs of the upper digestive system

SCCs of the upper digestive tract are the most common manifestation of bracken fern poisoning. Most cases occur in cattle between 7 and 8 years of age.

The main clinical sign is cough. Affected cattle have difficulty breathing and eating, resulting in weight loss, difficulty swallowing, food regurgitation (S34), halitosis, ruminal atony, chronic bloat (S34), and diarrhea. There may be an enlargement of the submandibular and prescapular lymph nodes (tumor metastasis) after a period of malnutrition. In a survey carried out in our laboratory (Souto et al.), tumors were found most frequently at the entrance to the rumen (45%) (S34,37), at the base of the tongue and pharynx (43%) (S34,35), and in the esophagus (12%) (S34,36). Metastases usually occur to regional lymph nodes (S38). Uncommonly, lung and liver metastases (S38) are seen in cases of pharyngeal and ruminal SCCs, respectively. Histological examinations of these tumors revealed them to be SCCs (S39). In the same anatomical regions where these tumors were found, numerous papillomas were also observed.

The involvement of bovine papillomavirus type (BPV-4) in the pathogenesis of SCC (S40) is also suggested. BPV-4 is epitheliotropic papillomavirus specific to the digestive system of cattle. In cattle with an uncompromised immune system, infection by BPV-4 is self-limiting because the immune response against papillomas is effective, and they regress approximately one year after infection. However, prolonged bracken fern grazing induces immunosuppression in cattle, and papillomas become florid and persist for a length of time, becoming the target for neoplastic conversion to SCCs (Campo et al. 1994).

Toxic principle

P. arachnoideum has antihematopoietic effects (bone marrow depression) and carcinogenic effects. The main carcinogens are a norditerpene glycoside called ptaquiloside and a flavonoid called quercetin. The involvement of BPV-4 in the pathogenesis of SCCs has also been suggested.

Diagnosis

The diagnosis can be confirmed by a significant amount of fern in the pasture as well as clinical signs and characteristic gross lesions. Clinical pathological examinations for the verification of anemia and thrombocytopenia together with histological examinations of bone marrow biopsies are important in diagnosing acute poisoning. However, treatment is not available.

Plants that induce heart failure

Ateleia glazioviana (no colloquial name in English)

Epidemiology

Poisoning by *Ateleia glazioviana* (S41) can cause cardiac failure, reproductive loss, and neurological disease in cattle. Toxicosis is related to the following:

i. fibrosis of the heart associated with sudden death or congestive heart failure;

ii. abortion or neonatal mortality, and

iii. myelinopathy associated with vacuolization (spongy state) of the nervous system.

There is considerable overlap between these three types of clinicopathological manifestations; the expression of each depends on the amount and duration of consumption of the plant.

A. glazioviana is a tree that can reach a height of 15 m but most often reaches 5-10 m. This deciduous tree has no leaves during the winter (from June to August). The leaves are palatable, but animals usually only ingest the leaves when forage is sparse due to drought or overgrazing (Gava & Barros 2001).

Poisoning causes abortion in cattle, sheep, horses, and probably goats (Gava et al. 2001). In bovines, abortion can occur at any time during pregnancy but usually occurs between November and May, when the animals ingest green leaves. Abortion sometimes occurs when livestock eat tree litter in the fall if the leaves are interspersed with grass. The frequency of abortion varies from 10% to 40% in pregnant cows. When ingestion occurs near the end of gestation and in a low amount, calves may be born alive, but newborns may be weak and often die within a few hours or days. Experimental studies in sheep showed that some lambs recovered (Raffi et al. 2004).

The neurological form of the disease occurs when hungry animals are introduced to a pasture with a large amount of plants (Gava et al. 2001). Morbidity and case fatality rates vary but can reach 30% and 20%, respectively (Gava & Barros 2001).

Cardiac disease occurs after the observation of neurological manifestations or in cases where no other previous clinical signs were observed. Both sporadic cases of sudden death or cardiac disease outbreaks may be observed. Most deaths occur in June and July (winter), probably due to the ingestion of leaves that fell to the ground (Gava et al. 2001).

Clinical signs and pathology

Heart failure caused by these plants manifests as a swollen and pulsating jugular vein with dependent subcutaneous edema (S42). Affected animals become easily fatigued and are isolated from the herd. Death can occur quickly, or animals can remain sick for many days or months. Some chronic cases experience terminal diarrhea. Some cattle die suddenly, without premonitory signals. At necropsy, the heart has white, irregular, and firm areas (S45). Subcutaneous edema, hydrothorax (S43), ascites, and edema of the mesentery and abomasal wall can be observed. The liver is chronically congested, with a nutmeg-like appearance (S44). Microscopically, myocardial fibrosis lesions predominate (S46). The liver exhibits severe centrilobular congestion associated with hepatocellular loss and fibrosis (nutmeg liver).

Abortion (S47) can occur at any stage of gestation. Cows present with some degree of lethargy for 1-3 days before abortion. Some cows are recumbent for long periods and occasionally suffer from blindness. In experiments with sheep, fetuses had the same characteristic cardiac and neurological lesions observed in adult cattle (Raffi et al. 2004). When the cows ingest the plant at the end of gestation, the offspring are weak and

unable to stand or suckle. Those that can stand up are lethargic and weak. Most die shortly after birth, but some recover (Raffi et al. 2004).

The neurological manifestation of *A. glazioviana* poisoning affects adult cattle at any age. The clinical signs are lethargy (S48), ataxia, head pressure, blindness, dry stools, low head carriage, and droopy ears. Some cattle remain in the recumbent position most of the time and are sometimes unable to raise their heads; others can stand but appear depressed for many days or weeks. Some animals experience severe weight loss and die after lying down for a few days. Others have recovered in 15-30 days. On electron microscopy examination, the lesion appears as intramyelinic edema resulting in *status spongiosus* (S49) or spongy degeneration (Raffi et al. 2006)

Toxic principle

The toxin in *A. glazioviana* has not yet been determined.

Diagnosis

A history of plant ingestion along with gross lesions in the heart and brain indicate the diagnosis.

Plants that cause muscle necrosis

Senna occidentalis (colloquial name: coffee senna**)**

Epidemiology

Ingestion of *Senna occidentalis* (S50) causes toxicity characterized by degenerative myopathy (Barros 1993, Carmo et al. 2011) in several livestock species, particularly cattle. This plant is found in grassland, land with fertile soil, or as a legume invader of soybean, corn, or sorghum fields. The seeds, pods, leaves and stems are toxic, but the beans are the most toxic. Poisoning occurs by ingesting cereal or hay contaminated with seeds or other parts of the plant. Poisoning also occurs in cattle grazing pastures invaded by the plant (Barros et al. 1999). Contamination of cereal grains occurs during the mechanical harvesting of crops in fields contaminated by *S. occidentalis*. This is particularly important when by *S. occidentalis* seeds contaminate sorghum fields because the seeds of both plant species are similar in size and density (Barros et al. 1990).

The disease generally occurs in the fall and early winter in cattle over one year old; outbreaks typically affect 10-60%, or rarely more, of the herd. Mortality is nearly 100%.

Clinical signs and pathology

In cattle, the disease begins with diarrhea 2-4 days after initial ingestion; diarrhea is occasionally accompanied by colic and tenesmus. Within a few days, signs of muscle dysfunction, such as muscle weakness, lack of coordination in the hindquarters, reluctance to move, and sternal or lateral decubitus, appear, and death can occur soon after. Some animals exhibit lethargy, anorexia, and weight loss, but it is common for cattle to remain alert during sternal recumbence(S51); some will continue to eat and drink until a few hours before death. The urine appears brown or reddish-brown due to the presence of myoglobin (S52).

As the disease progresses, there are sharp increases in serum creatine phosphokinase (CPK) and aspartate aminotransferase (AST) levels. Cattle can become sick two weeks after their last exposure to the plant.

Gross lesions appear as pale areas in the skeletal muscles, mainly in the large muscle masses of the hind- and forelimbs (S53). These areas may have multiple foci or appear as stripes, and they may be focally extensive or diffuse in a muscle group. Frequently, affected muscle groups are adjacent to healthy muscle groups. Cardiac lesions are mild or absent. The liver may be swollen, with accentuation of the lobular pattern. The urinary bladder may contain dark urine (myoglobinuria).

Microscopically, segmental, multifocal monophasic necrosis of the skeletal muscles can be observed. (S54). Centrilobular congestion associated with necrosis can be seen in the liver.

Toxic principle

The toxins in the plant have not been completely isolated or identified.

Diagnosis

Diagnosis is based on clinical signs and epidemiological and pathological examinations. Research should be conducted to confirm the source of the toxic plant in the forage or if the seeds contaminated the grains used for animal feed. Determination of serum CPK and AST levels aids in diagnosis.

The differential diagnosis (S55) should include other conditions associated with degenerative myopathies, such as intoxication by ionophore antibiotics, nutritional myopathy (vitamin E/Se imbalance), and downer cow syndrome (ischemic muscle necrosis). Among those four conditions, only nutritional myopathy will respond to treatment with vitamin E/Se.

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Table 1. A survey of 2,912 cattle necropsies was performed between 1990 and 2005 in the Veterinary Pathology Laboratory (LPV) of the Federal University of Santa Maria (UFSM), Rio Grande do Sul, Brazil. In 461 (15.83%) of these necropsies, poisonous plants were the cause of death. In this table, we present 5 out of the 19 species of plants involved in cattle deaths.

Plant	Common name	Percentage over 461 (%)
Senecio spp.	Ragwort or groundsel	56.14
Pteridium arachnoideum	Bracken fern	12.06
Ateleia glazioviana	No common name in English	10.31
Senna occidentalis	Coffee senna	2.63
Vicia villosa	Hairy vetch	1.54

Table 2. *Senecio* spp. poisoning in cattle. Clinical signs. (Source: Barros et al. 1992)

Frequent	Moderately frequent	Less frequent
Anorexia	Loss of weight (S14, S15)	Icterus
Separated from the herd	Neurological disturbances	Photosensitization
Rough hair coat (S14, S15)	Rectal prolapse (S16)	Dependent subcutaneous edema
Diarrhea (S14)	Sweet-sour odor from the skin and milk	
Tenesmus (S15)	Ascites (S14)	

Frequent = present in more than 60% of cases; moderately frequent = present in 20%-60% of cases; less frequent = present in less than 20% of cases

Table 3. *Senecio* spp. poisoning in cattle. Necropsy findings and histopathology (Source: Barros et al. 1992)

Frequent	Moderately frequent	Less frequent
Necropsy findings		
Very firm liver (S17, S18)	Ascites and hydrothorax (S19)	Icterus
Edema of the mesocolon (S20)	Edema of the mesenteric lymph nodes	Photosensitization
Edema of the abomasal folds (S21)	Polyps in the mucosa of the gall bladder	Hemorrhage in the serosa of the peritoneum
Distension of the gall bladder (S19)		Hydropericardium syndrome
Transmural edema of the gall bladder		
Histopathology		
Hepatic fibrosis (S22)	Spongy degeneration of the white matter (hepatic encephalopathy) (S23)	Random hepatocellular necrosis
Bile duct hyperplasia (S22)	Intranuclear acidophilic bodies in the hepatocytes (pseudoinclusions)	
Hepatomegalocytosis (S22)	Focal adenomatoid hyperplasia of the mucosa of the gallbladder mucosa	
Vacuolization of hepatocellular nuclei		
Edema of the gallbladder wall		
Edema of the submucosa of the abomasum		

Frequent = present in more than 60% of cases; moderately frequent = present in 20%-60% of cases; less frequent = present in less than 20% of cases