TRADITION AND MODERNITY IN VETERINARY MEDICINE, 2024, vol. 9, No 2(17): 70–76

ACUTE KIDNEY INJURY IN LLAMA (*LAMA GLAMA*) INDUCED BY OLEANDER INTOXICATION

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(Submitted: 5 June 2024; Accepted: 10 October 2024; Published: 25 November 2024)

ABSTRACT

A rare clinical case of an acute kidney injury after oleander leaves ingestion in llama (*Lama glama*) was the aim of the current report. Oleander (*Nerium oleander*) is a highly toxic plant and as little as 10 to 20 leaves can be lethal for an adult horse or cow. Despite the well –known arrhythmogenic effects of the oleander, manifesting in the case as a bradyarrhythmia, an acute kidney insufficiency with anuria was the key point. The patient demonstrated oliguria–anuria with extremely high creatinine blood level (up to 1167.0 μmol/l) for several days. Standard therapeutical regimen was followed, including fluid therapy. Despite the unfavorable prognosis, complete clinical recovery occurred.

Key words: kidney failure, azotemia, anuria, llama, oleander, intoxication.

Introduction

Oleanders that belong to the *Apocynaceae* family are often grown as ornamental evergreen shrubs in Southern Europe due to their lush flowering during summer. However, all parts of the oleander plant (*Nerium oleander*) are poisonous to humans and animals (Langford and Boor, 1996; Khordadmehr *et al.*, 2017). Accidental and/or experimental oleander toxicosis has been described in cattle, horses, sheep, goats, donkeys, rats, mice, rabbits, chickens; human cases have also been reported (Khordadmehr *et al.*, 2017). The ingestion of oleander leaves corresponding to only 0.005% of the animal`s body weight is often lethal (10 to 20 leaves for an adult horse or cow) (Galey *et al.*, 1996; Soto–Blanco *et al.*, 2006). The lethal dose of dried Nerium oleander leaves (LD) varies according to the animal species. Bovines are more sensitive compared to small ruminants, the LD being 50 mg/kg for cattle, 110 mg/kg for goats, and 250 mg/kg for sheep (Ceci *et al.*, 2020). Poisoning usually occurs accidentally due to contamination of food (Cheeke, 1998) as the high saponin content makes oleander unpalatable (Mack, 1984). Oleander is also toxic when dry. Risk factor for livestock can be exposure to clippings or to fallen and dried leaves (Galey *et al.*, 1996).

Major concerns include severe cardiac effects (Soto–Blanco *et al.*, 2006), gastrointestinal signs (Khordadmehr *et al.*, 2017; Tinelli *et al.*, 2023), hepatotoxicity (Khordadmehr *et al.*, 2017), nephrotoxicity (Khordadmehr *et al.*, 2017), neurological disorders (Rubini *et al.*, 2019). Anatomopathological findings consist of disseminated hyperemia and hemorrhages, multifocal coagulative necrosis of the cardiac muscle fibers, severe diffuse enteritis (Ceci *et al.*, 2020), hepatopathy, nephropathy, pulmonary congestion (Tinelli *et al.*, 2023). Animals exposed to oleander are often found suddenly dead (Galey *et al.*, 1996). *Exitus lethalis* may be observed within several hours to several days (Galey *et al.*, 1996; Ceci *et al.*, 2020).

The current study is dedicated to a rare case of oleander poisoning in a llama (*Lama glama*). The species is known as nutritionally adaptive even in areas where feed is relatively low quality

(Johnson, 1989); 48 to 75% of their diet consist of coarse bunchgrasses (Genin *et al.*, 1994) with specific preference for taller and coarser plants in the native South American environment (Johnson, 1989).

Keeping of llamas is becoming increasingly attractive in Europe (Neubert *et al.*, 2021); therefore, veterinarians should be acquainted with their specificities and expected problems.

Materials and methods

Study Animal

The object of the current study was a 6 years old female llama (app. weight 150–170 kg) from a mixed sheep farm in Botevgrad region (west Bulgaria).

Blood sample collection and laboratory tests

Blood samples (5 ml) were collected by cephalic venipuncture into 8 ml blood collection tubes with clot activator for serum and tubes with EDTA for CBC. Serum was separated by centrifugation (3500 rpm/min for 10 min) and tested *ex tempore*. CBC software on the analyzer for llama and alpaca species was used. Blood sampling was performed at regular basin (at D3, D5, D9, D12).

Complete blood count was performed by BC–2800 Vet (Mindray, China) automatic blood counting analyzer and for the serum biochemical assays semi–automatic biochemistry analyzer BA–88A (Mindray, China) was used.

The results of the main CBC and biochemical parameters are presented as mean value with standard deviation.

Therapy included licensed veterinary and human drugs in appropriate doses and regiment.

Results

Case history

The patient was a 6 years old female llama with a free roaming lifestyle in a 5 da yard. The intoxication was caused by an accidental ingestion of semi–fresh oleander leaves at Day 1 (D1) which was documented with a security camera in the farm. The presumed quantity consumed was ca. 5–10 leaves. The origin of the leaves was cut branches brought by wind from a neighbour property.

Clinical presentation and initial therapy

The first clinical sign was noticed by the owner app. 6–8 hours after the exposure: food refusal. The initial clinical examination established anorexia, adynamia, depression and moderate dehydration. Body core temperature was 37.8°C (RR – 37.5–38.9°C). Bradyarrhythmia on auscultation was detected – heart rate app. 30–40/min bpm (HR 60–90/min bpm). Respiratory rate was 18/min (RR 10–30/min).

The initial therapy included Atropine (Atropine Sopharma 1 mg/ml) and s.c. fluid therapy with 0.9 % NaCl solution (Natrium Chlorid Braun 0,9% solution for infusion).

At D2 oliguria was suspected and later confirmed.

At D3 blood samples for CBC and serum biochemical profile were obtained (Table 1). The laboratory tests demonstrated a severe leukocytosis (73.14 x 10^9/L, RR – 8.0–21.4 x 10^9/L) due to neutrophilia (69.49 x 10^9/L, RR – 4.7–14.8 x 10^9/L), as well as macrocytic and hyperchromic anemia. Serum chemistry analysis showed severe azotemia (elevated creatinine (1150.3 μmol/L, RR – 79.6–247.5 μmol/L) and urea concentrations (34.56 mmol/L, RR – 3.2–12.8 mmol/L) and increased

aspartate aminotransferase (>650 U/L, RR – 127–420 U/L) and creatine kinase levels (1191 U/L, RR – 14–238 U/L) (Fowler, 2010).

Table 1: Complete blood count and serum biochemical results of the case llama in dynamics of the clinical course

Parameter	unit	Ref*	D3	D5	D9	D12
WBC	10^9/L	8.2–16.5	73.14	33.55	49.14	50.25
LYM	10^9/L		2.63	1.17	1.57	1.46
MID	10^9/L		1.02	0.44	0.59	0.55
GRA	10^9/L		69.49	31.94	46.98	48.24
LYM%	%		3.6	3.5	3.2	2.9
MID%	%		1.4	1.3	1.2	1.1
GRA%	%		95	95.2	95.6	96
RBC	10^{12}/L	6.7–17.3	4.32	3.67	3.74	4.15
HGB	g/L	102–153	186	149	150	158
HCT	%	27–45	18.6	16	16	18
MCHC	g/L	330–410	992	928	938	882
MCH	Pg	8.6–13	42.9	40.5	40.2	38.2
MCV	fL	28–45	43.2	43.7	42.9	43.3
PLT	10^9/L		3200	2610	2443	2301
A/G			1.05	1.01	1.09	1.07
TP	g/L	39.0–75.0	77.8	66.3	56.9	65.4
ALB	g/L	17.0–37.0	39.8	33.3	29.6	33.8
GLOB	g/L	22.0–45.0	38.0	33.0	27.3	31.6
CREA	µmol/L	71.0–168.0	**1150.3**	**1167.0**	**238.1**	**232.9**
BUN	mmol/L	1.00–12.70	**34.56**	**38.77**	**8.65**	**9.21**
BUN/CREA		18.000–86.000	30.044	33.222	36.313	39.556
TB	µmol/L	0.0–5.0	1.6	1.5	2.0	4.8
ALT	U/L	10–29	41	25	15	19
AST	U/L	81–559	>650	>650	612	>650
AMY	U/L	175–1242	2223	1748	1668	1781
CK	U/L	11–153	1191	1395	168	79
GLU	mmol/L	4.72–13.11	13.04	9.48	8.79	9.15
TG	mmol/L	–	0.46	0.78	0.30	0.59
Ca	mmol/L	1.75–2.75	2.63	1.83	1.97	2.04
PHOS	mmol/L	0.32–3.55	2.41	3.24	0.90	0.98

**Reference range according to the analyzer software*

Clinical symptoms at D3–D5 were still anorexia, moderate depression and oliguria–anuria. After a four–day period of constipation hemorrhagic diarrhea developed at D4.

The therapy regimen included i.v. fluid therapy with saline and Furosemide (Furosemide 5% Alfasan) to force the diuresis. An antiobiotic therapy with Amoxicilin+clavulanic acid (Synulox®, Zoetis) was initiated because of the diarrhea and leukocytosis.

At D5 the control blood testing showed reduction of the leukocytosis, but progression of the anemia, azotemia and AST and CK activity (table 1).

In the next days (D6–D9) the llama became gradually bright and responsive, diuresis and urination frequency were normallized, feces consistency got better but there was still some blood. Fluid therapy was gradually decreased as well as the injection of the diuretic which was discontinued at D8.

The control blood testing at D9 and D12 showed normal nephron function but still elevated leukocyte count and AST level. Based on the results the antibiotic treatment was continued for few more days. During the main clinical course of the disease (around 10 days) the llama experienced a significant weight lost.

During the next 30 days, the llama remained alert, responsive, eating and drinking normally.

Discussion

Exposure to nephrotoxic substances is a significant factor for the development of an acute kidney injury (Barnett and Cummings, 2018). This is also relevant for the pathophysiology of kidney failure in large animals (Smith, 2009). The current report described the progress and outcome of a case of acute oleander intoxication in a llama. Oleander contains two main types of toxins–cardenolides and triterpenoids. The cardenolides are cardiac glycosides and can induce cardiotoxic effects, primarily as a result of Na+, K+–ATPase pump inhibition (Galey *et al.*, 1996; Tinelli *et al.*, 2023). The cardiac glycosides contained in N. oleander include oleandrin, folinerin and digitoxigenin (Joubert, 1989). The triterpenoids are considered irritants that can damage the digestive tract (Kozikowski *et al.*, 2009). The pathological effects in the current case were focused on kidney functions, heart, gastrointestinal and probably liver. However, the leading clinical manifestation was the renal failure. After the initial nonspecific signs of depression and anorexia, oligo–anuria and hemorrhagic diarrhea were observed. The dynamics of the azotemia resulted in a highest creatinine and urea serum levels five days after the exposure (Fig.1 and Fig.2). The clinical kidney injury last for about 6–7 days. A concordance between the anuria and the levels of azotemia was demonstrated.

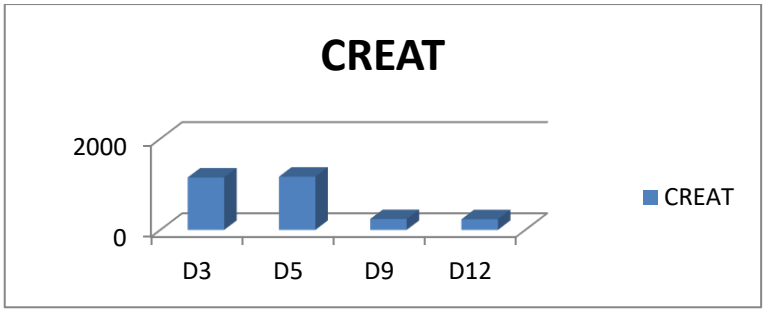

Figure 1: Creatinine level dynamics of affected llama

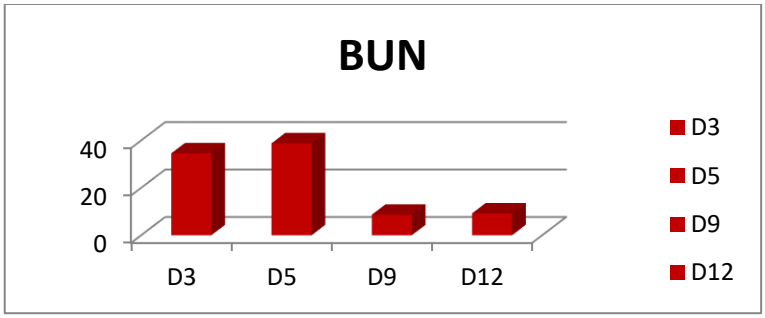

Figure 2: BUN level dynamics of affected llama

Significant laboratory abnormalities included severe leukocytosis; a white blood cell reaction typical for acute inflammatory response. A day after the detection of the white cell count elevation, enteritis developed. A link between the intestinal damage and the acute inflammatory response was concluded. The source for the increased aspartate aminotranseferase activity (which can be assumed as a moderate based on the reference range for llamas) could be due to damage of hepatocytes, skeletal or myocardial muscle cells (Han *et al.* 2022). Creatine kinase level elevation could be caused by skeletal muscle injury or myocardial breakdown (Panteghini, 1994; Sattler and Furll, 2004). In confirmation the affected animal demonstrated some cardiac signs (bradycardia) in the first two days. Between D5 and D9 the CK concentration was normalized despite the still elevated AST. Another possible explanation for the observed enzymes elevation can be liver lipidosis. Common factors for lipidosis in llama are anorexia and recent weight loss (Tornquist *et al.* 1999, Tornquist *et al.* 2001).

Clinical signs observed in cattle may develop after a delay of 2–4 hours and may include depression, anorexia, abdominal pain, weakness, rumen atony, diarrhea, nasal discharge; excessive salivation, bradycardia or tachycardia, weak and irregular pulse, heart blocks, ventricular arrhythmias; excitement, intermittent convulsions, dyspnea, and coma may precede death (Galey *et al.*, 1996; Ceci *et al.*, 2020). The clinical course in sheep and goats is similar – heart and kidney damages were mainly developed (Barbosa *et al.*, 2008; Ozmaie *et al.*, 2013).

In a retrospective study of oleander intoxication in 11 llamas and 1 alpaca 9 out of 10 animals had evidence of acute renal failure, 7 had gastrointestinal signs, and 4 had cardiac dysrhythmias on initial evaluation; the overall mortality rate was 25%, but the mortality rate for the 10 camelids that were medically treated was 10% (Kozikowski *et al.*, 2009).

Oleander toxicosis should be considered a differential diagnosis in sick camelids; it is often observed as a herd problem but prognosis can be fair to good if treated promptly (Kozikowski *et al.*, 2009).

Conclusion

Acute renal injury due to oleander toxicosis should be suspected in adult llamas with a history of exposure to oleander plants that are presented with depression, anorexia, diarrhea, cardiovascular signs and severe azotemia. The presence of marked inflammatory changes in the CBC, and severe azotemia are the keystones in the laboratory alterations. Initial therapy should focus on rehydration and promotion of the diuresis, and also prevention of secondary bacterial infections. Oleander toxicosis should be considered a differential diagnosis in camelids with acute kidney failure.

Acknowledgement

We can really appreciate the excellent cooperation of Eng. Valentin Nikolov, PhD – the owner of the llama patient whose efforts were decisive.

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