A urinary retention syndrome in beef cows probably caused by ingestion of *Cistus salvifolius*

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Two outbreaks of a urinary retention syndrome in beef cattle grazing in northern Israel and probably caused by ingestion of the shrub *Cistus salvifolius* are described. Consumption of *Cistus* shrubs occurred during a period of pasture scarcity in the years 1998-2000. A progressive syndrome of wasting, apathy, anorexia, distention of the urinary bladder, dysuria, nephrosis, constipation and recumbency, culminating in death, was seen. In one herd, a high mortality rate of 58.8% (20/34) in first and second calving cows in comparison to 5.4% (4/74) in adult cows was noted. Typical clinical-pathological findings revealed increases in blood urea, creatinine, aspartate aminotransferase (AST), creatine kinase (CPK) and lactate dehydrogenase (LDH). Decreases were found in alkaline phosphatase (ALP), total serum protein, albumin (ALB), potassium (K), sodium (Na) and chloride (Cl). No significant changes were noted in levels of gamma glutamyl transferase (GGT), calcium, triglyceride and cholestrol levels. The main pathological findings were severe cystitis, pyelonephritis and a great increase in urine bladder wall thickness. On the basis of epidemiology, clinical signs, clinical-pathological, and pathological and histopathological findings, a diagnosis of *Cistus salvifolius* toxicosis was made.

**SUMMARY**

Un syndrome de rétention urinaire chez des bovins dû à l’ingestion de *Cistus salvifolius*. Par I. YERUHAM, U. ORGAD, Y. AVIDAR, S. PERL, M. LIBERBOIM, H. ADLER et A. SHLOSBERG.

Cette étude décrit deux épisodes d’un syndrome de rétention urinaire chez des bovins qui paissent dans le nord d’Israël, dus probablement à l’ingestion d’un arbuste, *Cistus salvifolius*. La consommation d’arbuste du genre *Cistus* s’est produite au cours d’une période de pénurie d’herbe dans les années 1998-2000. Il a été observé un syndrome progressif de dépérissement avec apathie, anorexie, distention de la vessie, dysurie, néphrose, constipation et décubitus conduisant à la mort.

Dans un troupeau, un taux de mortalité élevé de 58,8 % (20 animaux sur 34) a été enregistré sur des vaches au premier ou second vêlage par rapport à 5,4 % de mortalité (4 animaux sur 74) sur des bovins adultes.

Les analyses biochimiques sanguines montrent une augmentation de l’urée, de la créatinine, de l’aspartate aminotransférase (AST), de la créatinine kinase (CK) et de la lactate déshydrogénase (LDH) et une diminution de l’alkaline phosphatase (ALP), des protéines totales du sérum, de l’albumine (ALB), du potassium (K), du sodium (Na) et du chlore (Cl). Aucun changement significatif n’est noté dans les taux de gamma glutamyl transférase (GGT), de calcium, de triglycérides et de cholestérol.

Les lésions révélées par l’autopsie sont : une sévère cystite, une pyélonéphrite, un important épaissement de la paroi vésicale.

Sur la base de l’épidémiologie, des signes cliniques, de la pathologie et de l’anatomie pathologique, le diagnostic d’intoxication par *Cistus salvifolius* fut établi.

**KEY-WORDS :** urinary retention - beef cows - *Cistus salvifolius* - toxicosis.

**MOTS-CLÉS :** rétention urinaire - bovins - *Cistus Salvifolius* - intoxication.

Trees and shrubs in arid environments are often important feedstuffs for ruminants, but their usefulness to grazing animals is often limited by the presence of toxins, such as phenolic compounds including tannins, which can adversely affect feed intake, digestibility and or even cause toxicosis. Twenty *Cistus* spp. shrubs (*Cistaceae*, rockrose family) grow in the Mediterranean region, but only two species, *Cistus salvifolius* (sage-leaved cistus) and *C. creticus*, are found in the eastern Mediterranean.
within a single plant species according to seasonal changes in leaf morphology, moisture content, and chemical composition [4, 11]. Tannins are a very complex group of plant anti-nutritional metabolites that are distinguished from other polyphenolic compounds by their ability to precipitate proteins. Their major negative effect results from either direct inhibition of digestive enzymes, or from formation of indigestible complexes with endogenous proteins [22]. Tannins are converted by bacterial fermentation in the rumen to gallic acid and pyrogallol, both known to be nephrotoxic [10, 19, 20].

In ruminants ingesting tannins, supplementation of polyethylene glycol (PEG) increased digestible organic matter intake, which was associated with a marked improvement in protein and cell wall digestibility [22]. PEG is a polymer that binds tannins irreversibly over a wide range of pH (2-8.5) and its presence reduces the formation of protein-tannin complexes [12]. The present report describes the clinical, laboratory, and pathological findings concerning presumed *Cistus salvifolius* toxicosis in 2 beef cattle herds grazing in the northern hills of Israel.

**Case report**

**A) HISTORY**

One herd (Herd A) comprised an average of 54 mixed-breed beef cattle kept in a natural hilly pasture in the Carmel hills in Israel. The heifers were kept in barns until post-calving, and than were transferred to the pasture. During the summer months (June-November), the owner supplemented the drinking water with Polyethylene glycol (PEG) at a dosage of 40 g/head per day. During 2 observation years (1998-1999, 1999-2000) animals started to show clinical signs and mortality in the autumn-winter months (November-February). The syndrome was only seen in females. In the course of the illness, clinical examinations were conducted and blood samples were collected from 6 animals exhibiting the syndrome. Blood samples taken from grazing clinically healthy grazing animals in a neighboring herd [2] serve as a comparison.

The second herd (Herd B) grazed for the first time, on a rocky, hilly area in the far north of Israel and after several months the clinical syndrome was seen from about December-April.

**B) LABORATORY PROCEDURES**

Clinical-pathological, urine analysis and haematological examinations were performed on affected animals, and post-mortem examinations were carried out on 4 cows in Herd A. Specimens of liver, lung, kidney and alimentary tract were collected in 10 % neutral buffered formalin. Sections were stained with haematoxylin-eosin and examined by light microscopy.

The blood samples were collected by means of jugular venipuncture, into plain evacuated tubes for recovery of serum and into EDTA-containing tubes for complete blood count (CBC). The serum was separated and analyzed within 24 h. Enzymes, metabolites and minerals were analyzed spectrophotometrically with a Kone Selective Chemistry Autoanalyser (Kone Corporation, Finland) at 30°C, according to standard methods. The following enzymes were determined: aspartate aminotransferase EC 2.6.1.1 (AST); lactate dehydrogenase EC 1.1.1.27 (LDH); alkaline phosphatase EC 3.1.3.1 (ALP); creatine kinase EC 2.7.3.2 (CPK); gamma-glutamyltransferase EC 2.3.2.2 (GGT). The following metabolites were determined as indicated: urea, enzymatically; creatinine colorimetrically; albumin and protein, colorimetrically; globulin by subtracting albumin from total protein; and triglyceride, colorimetrically. Sodium (Na), potassium (K) and chloride (Cl) were determined by means of a Kone Selective Ion Analyzer (Kone Corporation, Finland). Calcium (Ca) and inorganic phosphorus (Pi) were determined colorimetrically, respectively. [26]. Urine samples were collected via free catch in specimen cups and stored as 4°C awaiting analysis for urinary calculi and bacteriological examination. The urine samples were inoculated onto 5 % sheep blood agar, nutrient agar and McConkey agar (Difco laboratories) and incubated overnight at 37°C. CBC and differential counts were performed by standard procedures, with the Technicon H1 System (Miles Inc; Diagnostics Division, Tarrytown, NY).

Statistical analysis was performed with the SAS software (21), with differences between the comparison group and affected group being considered significant at p < 0.05.

**C) CLINICAL FINDINGS**

In Herd A, the condition of the first and second calving cows deteriorated markedly, and ultimately the mortality rate reached 58.8 % (20/34) in comparison to 5.4 % (4/74) in adult cows (Table I). The progressive syndrome seen in both herds comprised manifestations of apathy, anorexia, decreased rumen motility and cessation of rumination. Persistent elevation of the tail head in many cows was often accompanied by difficulty in urination, with dribbling of drops of urine, or a persistent low volume stream of urine, with no straining, being typical; rectal examination invariably revealed a full urinary bladder. Dehydration was seen with moderate subcutaneous oedema under the jaw and on the ventral abdomen. Dry rough coats, crust on muzzle and constipation were also observed. Rectal temperature of all examined animals was normal, but heart and respiratory rates were usually elevated (95-110 beats/min and 50-70 breaths/min). Once severe urinary difficulties were apparent, there was a rapid weight loss, culminating in recumbency, severe cachexia and death.

Examination of the pasture in Herd A revealed very high consumption of both *Cistus salvifolius* and *C. creticus* bushes. In the pasture of Herd B, only *C. salvifolius* was present.

**D) BIOCHEMICAL, BACTERIOLOGICAL AND HAEATOMATOLOGICAL FINDINGS**

The biochemical findings of the affected animals in Herd A are presented in Figures 1-5, and with data from clinically
healthy animals at the same age, and breed from a neighboring herd for comparison. Marked increases in LDH (3070 ± 476 SD compared with 2307 ± 34 in the normal herd) (P < 0.05), CPK (1486 ± 1918 vs 219 ± 73 U/L) (P < 0.001) (Fig. 1), and AST (133 ± 76 vs 76 ± 17) (P < 0.001) (Fig. 2). A decrease was found in ALP (118 ± 43 vs 286 ± 147 U/L) (P<0.01) (Fig. 2). Increase in blood urea (105 ± 53.3 mg/dl) in comparison with the normal herd (49.4 ± 12.2 mg/dl) (P<0.001) (Fig. 3), and the same pattern was noted also with creatinine (3.89 ± 1.94 vs 1.22 ± 0.15 mg/dl) (P < 0.001) (Fig. 4). Decreases in total proteins (72 ± 2 vs 81.7 ± 3 gr/dl in the normal herd) (P<0.01); albumin (33±1 vs 36.5±2 gr/dl) (P < 0.01); and globulin (39 ± 3 vs 45.2 ± 4.5 gr/dl) (P < 0.01) (Fig. 5) were noted. Calcium decreased slightly (8.6 ± 1.0 vs 9.57 ± 0.54 mg/dl in the normal herd). No significant changes were noted in the GGT, triglyceride and cholesterol levels. Comparison among the levels of minerals and electrolytes revealed decreases in K, Na, and Cl compared with the normal herd (4.66 ± 0.46 vs 5.69 ± 0.15; 139 ± 4.0 vs 142 ± 2.1; 93.7 ± 4.3 vs 107.6 ± 4.3 mmol/l, respectively) (P < 0.01) and increase in Pi (9.33 ± 0.82 vs 7.24 ± 0.3 mg/dl) (P < 0.01) (Fig. 4). Urine samples were dark yellow and of moderate specific gravity (1.025 on average) and urine pH was 7.6 on average. The urine contained 100-300 mg/100ml protein. Microscopic examination of the urine sediment revealed crystals of triple phosphate and moderate quantity of erythrocytes. Bacterial cultures of urine samples were negative. Haematology did not reveal any consistent abnormalities.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>First &amp; second calving cows</th>
<th>Adult cows</th>
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</thead>
<tbody>
<tr>
<td>1998/1999</td>
<td>10/14 (71.4 %)</td>
<td>2/36 (5.5 %)</td>
</tr>
<tr>
<td>1999/2000</td>
<td>10/20 (50 %)</td>
<td>2/38 (5.3 %)</td>
</tr>
<tr>
<td>1998/2000</td>
<td>20/34 (58.8 %)</td>
<td>4/74 (5.4 %)</td>
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**E) PATHOLOGICAL AND HISTO-PATHOLOGICAL FINDINGS**

The most prominent pathological findings at necropsy were consistently an urinary bladder that was greatly distended and filled with a turbid haemorrhagic urine. The bladder wall was thickened and very hyperaemic with a irregular mucosal surface (Fig. 6). Kidneys were slightly enlarged, had an irregular surface with yellow, pale foci randomly scattered over the surface but more abundant in the poles of the kidneys and showed a mild interstitial nephritis. Histopathology of the kidneys revealed a severe, subacute, diffuse neutrophilic pyelonephritis (Fig 7). In the urinary bladder the transitional epithelium was absent in most areas and was replaced by necrosis and inflammation. The *propria mucosa* was infiltrated by mixed inflammatory cells mainly lympho-plasmocytes, some histiocytes and a few neutrophils (Fig. 7).

In the mucosa of the small intestine a moderate, diffuse, subacute to chronic enteritis was observed. The majority of
inflammatory cells were lympho-plasmocytes and numerous eosinophils were also present. No significant histopathological lesions were seen in all the other tissues examined including the brain and entire length of the spinal cord.

**Discussion**

Despite the relatively high widespread of *Cistus* spp. in the Mediterranean basin there has been only one other case of suspect *Cistus* toxicosis in cattle [15]. The flowering period of *C. salvifolius* is between March and June. The Habitat is on garigue, rocky places on limestone soils. All *Cistus* spp. should be regarded as potentially toxic because of their relative high tannin concentration. The tannin concentration in *Cistus* spp. in Israel is about 25% of the dry matter (GILBOA, personal communication). The effects of heavy consumption of *Cistus* spp. apparently due to the supplement of PEG in the drinking water [22], in the late autumn and at the beginning of the winter (October-December), when pasture was sparse, aggravated by insufficient supplemental feeding, may have been the cause of the toxicosis in Herd A. The daily supplementation of PEG increase the intake and digestion of tannin-containing leaves [22]. The affected animals developed a chronic course of debilitating disease. This disease lasted for several weeks after removal of the animals from the *Cistus* source. The condition was not diagnosed as having any involvement with an infectious or metabolic diseases.

The duration of the toxicosis seemed to vary with the amount of toxin ingested, as reported in a previous toxicosis [26]. The cattle in the present study were suspected of having been exposed to a toxic agent, and the pastures were thoroughly examined for the presence of known toxic annual and perennial plants, chemicals or non-made artifacts, but no
plausible cause was found. As Herd A was on sparse pasture and no supplementary feed had been given, except the PEG in drinking water, it is believed that the herd lacked access to sufficient feed and thus were forced to eat native shrubs and bushes. Only *Cistus* spp. were considered to be sufficiently toxic to induce such a syndrome, especially when the climatic conditions during 1998-2000, possibly caused on increase of tannins concentrations in the *Cistus*. The mode of elimination of PEG - tannin complexes from the intestine are still uncertain. Possibly these complexes may contribute also to the nephrotoxicosis. The condition of affected animals deteriorated markedly, and the mortality rate reached 58.8 % for the first and second calving cows and only 5.4 % for the adult cows. It seems that young cattle are more susceptible to oak toxicosis [5, 6, 16, 26]. Urinary retention, the incomplete emptying of the bladder, may be caused by failure of contractile function, inappropriate outlet resistance, or both [13]. No evidence was found for physical or anatomical causes, unlikely anyway in many cows simultaneously. No histopathological lesions were found in the spinal cord to indicate a central effect. Phenolic compounds may block pudendal nerves [13], and manipulation of pudendal nerve activity has been attempted to reduce striated urethral muscle resistance. This is probably the reason for the urinary retention and distended urinary bladders found in the affected animals.

The clinical signs, macroscopic and microscopic lesions closely corresponded to those described in cattle succumbing to oak toxicosis [5, 6, 16, 26]. The nephrotoxicosis might be attributed to a peracute decrease in glomerular filtration rate and oliguria [24] caused by renal changes elicited by ischaemia and the nephrotoxic nature of tannins and their metabolites [1, 28], or secondary to the pathological accumulation of urine in the bladder.

Our findings provide evidence that renal damage, paralysis of the urinary bladder and uremia may be the cause of death in Cistus toxicosis since striking elevations of the urea and creatinine levels, like those associated with nephrosis, were found. It has been stated that only after extensive loss of 50-60 % of glomerular function will serum urea and creatinine concentrations increase [24], which means that increases in serum concentrations of creatinine and urea are sensitive indicators of partial renal dysfunction [23]. Serum creatinine concentration is usually considered a more accurate indicator of renal function in ruminants than urea concentration, because the normally functioning rumen recycles urea by using it a nitrogen source for bacterial protein synthesis [17]. This microbial activity decreases or disappeared as a secondary effect of renal diseases and prolonged anorexia [17]. The marked increase in urea concentration found in the affected cattle in the present outbreak is an important finding, implying decreased urea clearance by rumen and kidneys, and it supports the role of renal failure in the pathogenesis of Cistus toxicosis similar to the condition in oak toxicosis. Blood urea and creatinine estimations have also been of prognostic value [17, 24]. Decreases in sodium and chloride also occur in renal disease [26]; decreases in plasma concentrations of these electrolytes are a result of excessive loss through kidney or decreased reabsorption in the glomerulus. In the present survey decreases in sodium and chloride concentration were moderate, compared with the normal group. Polyuria, low urine specific gravity and proteinuria also contributed to clinical deterioration and ultimately to death.

Elevations of AST, CPK and LDH were apparently due to muscle damage consequent to recumbency of the affected animals [2]. The decrease in total protein concentration was due to hypoalbuminaemia resulting from albumin loss in the kidney («nephrotic syndrome») [2]. Malabsorption was most probably the reasons for the decreases in alkaline phosphatase and albumin levels [2]. Inorganic phosphorus was reabsorbed from the glomerular filtrate by the renal tubules,
even though the increase in serum concentration was not significant. It can indicated tubular dysfunction and it is a useful diagnostic indicator of the development of renal disease [2, 23]. Hypocalcaemia has been reported in cases of chronic renal failure [2], and could also be a result of hypocal-buminemia.

Supplementary feeding with hay and further consideration of supplementation with PEG may be beneficial and cost effective especially when there is pasture scarcity. Presumptive diagnosis of Cistus toxicosis was made, based on a herd history of exposure to Cistus shrubs, physical findings of the sick animals, clinico-pathological data consistent with renal dysfunction, results of urine analysis, and gross and microscopic kidney lesions (renal tubular necrosis).

This clinical diagnosis indicates that these should be an increased awareness that Cistus toxicosis may occur in cattle in the Mediterranean region. It is strange that such an obvious clinical syndrome had not been recorded previously in the Mediterranean basin, apart from one report from Portugal, at the opposite, far side of the Mediterranean [15]. The cases in Portugal occurred in the same years as these cases, but were the opposite, far side of the Mediterranean [15]. The cases in Portugal occurred in the same years as these cases, but were more chronic in nature, and were not always fatal; probably less tannins or some other toxic components were ingested.

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