NOTE *Internal Medicine*

Xanthine Nephrolithiasis in a Galician Blond Beef Calf

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ABSTRACT. A six-month-old female Galician Blond beef calf presented signs of apathy, anorexia and weight loss. The analysis of a blood sample confirmed renal failure. Bilateral nephrolithiasis was diagnosed at necropsy. Quantitative analysis revealed the nephroliths to be composed of 100 per cent xanthine. In cattle, xanthinuria has only been described in the Japanese Black breed, but never before in other breeds. Clinical history suggested a naturally occurring xanthinuria.
KEY WORDS: calf, cattle, Galician Blond, nephrolithiasis, xanthine.

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Xanthinuria is a rare metabolic disorder caused by accumulation of xanthine in blood and urine, which can lead to health problems such as renal failure and xanthine kidney stones. Two forms of the disease have been described, congenital (primary) and iatrogenic (secondary). In human beings, the primary or naturally form is an inborn enzymatic defect of xanthine dehydrogenase (XDH) with an autosomal recessive mode of inheritance that results in xanthinuria and xanthine calculi accumulation in kidneys. This enzyme catalyses the conversion of hypoxanthine to xanthine, and xanthine to uric acid [10]. The iatrogenic or secondary form is the most frequent form in small animals. It is usually associated with the administration of allopurinol as part of the medical management for urate urolithiasis [6]. Naturally occurring xanthinuria has been reported only rarely in dogs, including a family of Cavalier King Charles [13] and Dachshunds [1, 3], and in cats [9, 12, 15].

In cattle, xanthinuria was demonstrated in the Japanese Black cattle breed [2, 5] and this form of bovine xanthinuria has been shown to be, as in humans, an autosomal recessive disorder characterised by a congenital deficiency in XDH [14]. As far as we know, xanthinuria has only been reported as an outbreak in the Japanese Black cattle breed [2, 5], but never before in other breeds and/or as an individual case in cattle. In this report we describe a case of naturally xanthine urolithiasis in a Galician Blond beef calf.

A six-month-old female beef calf of Galician Blond breed was referred to the Farm Animal Service of the Veterinary Teaching Hospital Rof Codina, University of Santiago de Compostela, Spain. The calf was reared outdoors in a small farm with two adult reproductive dams, and feed consisted mainly of mother's-milk and local forage (fresh pasture or hay). The primary complaint was apathy, anorexia, weight loss and hair bristling lasting one week. The clinical examination findings were considered unremarkable; therefore a deworming treatment with fenbendazole (Panacur® 10 suspension, Intervet Shering-Plough Animal Health, Spain) at 5 mg/kg per *os* once a day for 5 days had been prescribed. One week later the health of the calf got worse and the animal became more apathic. The clinical examination did not reveal any clear alteration, but the results of a complete blood count and serum biochemical analysis (Table 1) revealed severe azotemia, elevated levels of aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and phosphorus, and low levels of calcium and magnesium. Urianalysis revealed mild haematuria (2+) and pH of 8. No crystals or bacteria were found on sediment examination.

The calf had been rehydrated with Ringer lactate solution (Ringer Lactate, B Braun, Barcelona, Spain) at 50 m*l*/kg/24 hr for 2 days, and had been treated with amoxicillin (Amoxzel® suspension, Intervet Shering-Plough Animal Health, Spain) at 10 mg/kg IM once a day for 3 days; but it did not respond to the therapy and 3 days later, levels of cre-

Table 1. Blood analyses

Parameters	Patient	Normal Range [11]
RBC ($\times 10^6/\mu l$)	7.40	5–10
Hb (g/d*l*)	8.90	8–15
PCV (%)	32.0	24–46
WBC ($\times 10^3/\mu l$)	11.2	4–12
Platelet count ($\times 10^3 \mu l$)	325	100–800
Total protein (g/d*l*)	6.8	6.7–7.5
BUN (mg/d*l*)	>130	20–30
Creatinine (mg/d*l*)	>13.6	1–2
Glucose (mg/d*l*)	55	45–75
Calcium (mg/d*l*)	7.3	9.7–12.4
Phosphorus (mg/d*l*)	8.4	5.6–6.7
Magnesium (mg/d*l*)	0.52	1.8–2.3
AST (IU/*l*)	171	43–127
AP (IU/*l*)	85	27–107
GGT (IU/*l*)	24	15–39
CPK (IU/*l*)	587	105–409
LDH (IU/*l*)	>2800	697–1445

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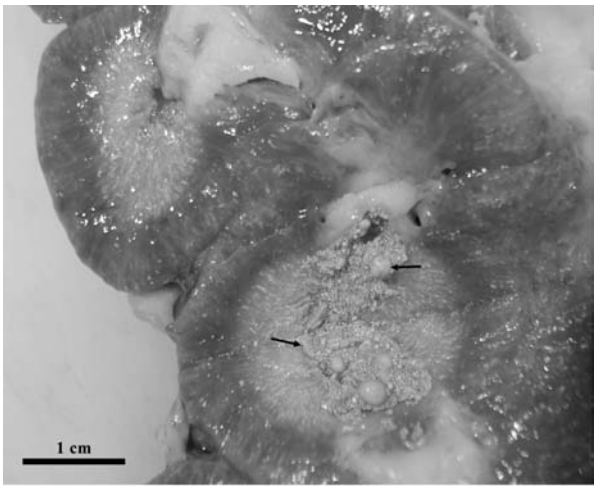

Fig. 1. Cut surface of kidney containing golden to brownish yellow and different sizes calculi (arrows) localized in the calyx and pelvis renalis.

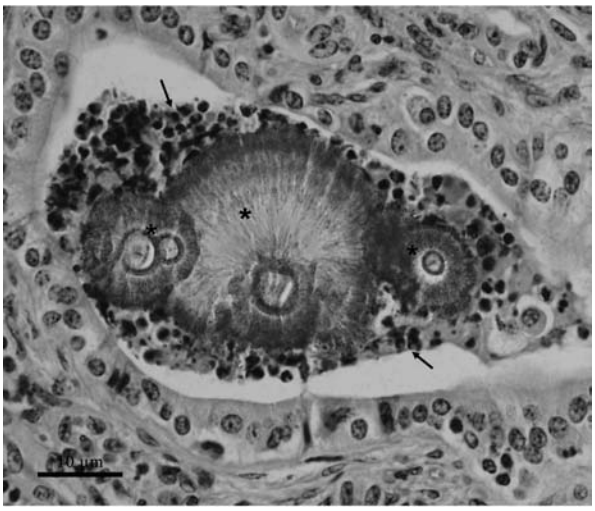

Fig. 2. Histological appearance of crystals (asterisks) in the lumen of renal tubules, accompanied by rests of necrotic epithelial cells (arrows).

atinine and BUN were higher than before. Due to no treatment response and the worsening of its condition the calf was rapidly euthanized.

Bilateral nephrolithiasis was diagnosed at necropsy. The kidneys had turned yellowish and the section showed a golden slightly granular small or sand-like material which was laid out in the form of radial striations in the cortex and more intense in the medulla (Fig. 1). Histopathology revealed crystals with a pinkish colour in the centre and a disposition in concentric layers and externally a radial disposition, contained mainly in the collecting and distal uriniferous tubules in the renal medulla. Some of the epithelial tubular cells presented necrosis and destruction caused by uroliths (Fig. 2). Fibrous tissue proliferation and mononuclear inflammatory cell infiltrations usually covered the stones. Calculi were also found in pelvis renalis lumens. The surface of the calculi was smooth and glossy, and one of them was submitted to the Minnesota Urolith Center (University of Minnesota, 1352 Boyd Avenue, Saint Paul, MN 55104) for quantitative mineral analysis. The analysis revealed the nephroliths to be composed of 100 per cent xanthine.

Previous reports of xanthine uroliths in cattle of Japanese Black breed were characterized by elevated xanthine secretion in the urine [2, 5], low blood and urine uric acid concentrations and low activity of xanthine oxidase in tissues (liver, spleen, kidney and small intestine) [2]. Animals showed symptoms at early age (between 1–6 months) [2], with lethal growth retardation at approximately 6 months [5]. Affected cattle had expanded renal tubules containing xanthine calculi ranging from 1–3 mm in diameter [2, 5, 14]. More than 300 xanthinuria-affected cattle have been recorded in the last twenty years in Japan and it was confirmed that all parents were descendants of a putative founder sire [14]. Pedigree analysis in that herd indicated, as in humans, that bovine xanthinuria is inherited as an autosomal recessive trait by which affected cattle lose XDH [14]. Similarly, in a family analysis of Cavalier King Charles spaniels with xanthinuria, the disorder has been demonstrated to be inherited in an autosomal recessive mode [13].

In the present case there is no information on blood and urine examination for purine metabolism since we did a post-mortem diagnosis, but clinical history suggested a naturally occurring xanthinuria, presumably due to a deficiency in xanthine dehydrogenase. Definitive diagnosis of naturally occurring xanthinuria based upon plasma and urine uric acid concentrations are characteristically very low, xanthine high and low or no activity of the enzyme XDH [2, 9, 15]. Another possibility to confirm the disease is to examine the family line: siblings, sire and the dam, but unfortunately the dam had been slaughtered one week prior the calf was euthanized, and there were no siblings. The calf was born by artificial insemination from a Galician Blond sire which was no longer alive. The association of Galician Blond breed has investigated for possible occurrence of urinary troubles in their offspring, but none of them had suffered from urinary disease; nevertheless they are aware of in the necessity of having a strict control in the sire's offspring. Similarly to the xanthinuria outbreak in the Black Japanese breed [2, 5], clinical symptoms started at 6 months age, although in our case the laboratory findings also suggest a xanthinuric myopathy, with elevation of muscle markers enzymes (ASAT, CK and LDH).

In cattle, urinary stone formation is mainly induced by inappropriate composition of the fodder [7]. These circumstances occur especially in feedlots with fattening cattle receiving rations with a high content in cereal grains, oil meals, limited water intake and an excess of phosphorus and magnesium with relatively low levels of calcium and potas-

sium, predisposing the disease to occur [8, 11]; and struvite (magnesium ammonium phosphate) or calcium phosphate (apatite) calculi are typically developed. Other less frequent types of calculi include those composed of silica, carbonates or oxalates described in livestock grazing in areas that contain large quantities of these minerals [7, 11]. Bovine xanthinuria is recognised to be an extremely uncommon metabolic disorder; in fact calculi of xanthine were not described in the literature [4, 8, 11]. It is important to take into account that in clinic of farm animals it is not common to do blood analysis or necropsy, and urolithics analysis are even less common, so most times diseases are not diagnosed. Although the incidence of bovine urolithiasis has decreased worldwide in recent years because of the improvement in the management of cattle [4, 8, 11], it is very interesting to do the analysis of the mineral composition of the uroliths in order to know the prevalence of calculi. In conclusion, this is the first individual clinical case of xanthinuria in other breed of cattle, so xanthinuria is not only an inherent problem of the Japanese Black cattle breed.

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