Renal medullary rim sign in 2 adult quarter horses

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Abstract — This report describes a renal ultrasonographic abnormality (medullary rim sign), which was identified in 2 separate cases of spontaneously occurring disease associated with chronic and acute overdosage of phenylbutazone therapy. In horses, medullary rim sign has only been documented in neonatal foals experimentally administered large doses of phenylbutazone.

Résumé — Bande corticomédullaire hyperéchogène rénale chez 2 quarter horses adultes. Ce rapport décrit une anormalité ultrasonographique du rein (bande corticomédullaire hyperéchogène) identifiée dans 2 cas séparés de maladie spontanée associée à une surdose chronique et aiguë de phénylbutazone. Chez le cheval, le signe de la bande corticomédullaire hyperéchogène n'a été documentée que chez les poulains nouveau-nés auxquels on avait administré expérimentalement de fortes doses de phénylbutazone.

(Traduit par docteur André Blouin)

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Case 1

A 10-year-old, 430-kilogram, quarter horse gelding was referred to the veterinary teaching hospital at Louisiana State University for evaluation of anorexia, weight loss, ventral edema, and intermittent colic. By the owner's estimation, the gelding had lost approximately 90 kg. Historically, the gelding had been treated with phenylbutazone (2 g, PO, q12h) for 2 y, following diagnosis of navicular disease.

The gelding was thin, but otherwise normal, on physical examination at the time of admission. No abnormalities were detected via palpation per rectum.

A complete blood cell count (CBC) and serum biochemical profile revealed mild anemia (packed-cell volume 0.28 L/L; reference range: 0.35–0.50 L/L), hypoproteinemia (36 g/L; reference range: 60–80 g/L), and hypoalbuminemia (13 g/L; reference range: 30–41 g/L). Urinary gamma-glutamyl transferase to urinary creatinine (uGGT:uCR) ratio was 53% (reference range: <25%). Urinalysis, abdominal fluid analysis, and urinary fractional excretion of electrolytes were normal.

Gastroscopic examination revealed mild mucosal ulceration and erosions throughout the nonglandular portion of the stomach along the *margo plicatus*. Ultrasonic examination of the abdomen was performed by using a real-time mechanical sector scanner with a 7.5 MHz and 5.0 MHz transducer (Ausonics Opus 1, Ausonics, Sydney, Australia). During real-time examination, the kidneys were subjectively normal in size and shape, with smooth serosal margins. The left renal cortex was hypoechoic to the spleen and hyperechoic to the renal medulla. The echogenicity of the right kidney was similar to that of left kidney. However, in both kidneys, a distinct curvilinear hyperechoic band was observed, parallel to the corticomedullary junction (medullary rim sign; MRS) (Figures 1 and 2). No other renal abnormalities were observed. Both the increased uGGT to uCR ratio and the renal ultrasonographic changes were suspected to be secondary to renal dysfunction, resulting from the previous long-term phenylbutazone administration. Based on the history of phenylbutazone administration, the clinical signs, and clinicopathological data consistent with protein-losing enteropathy, we made a provisional diagnosis of right dorsal ulcerative colitis. The gelding was discharged with recommendations to avoid the administration of nonsteroidal antiinflammatory drugs (NSAIDs), to feed a complete pelleted concentrate containing at least 30% dietary fiber (Purina Horse Chow 200, Purina Mills, St. Louis, Missouri, USA), and to eliminate roughage from the diet. Other recommendations were to feed the concentrate at frequent intervals, to add pysillium mucilloid (Equisyl, Animal Health Care Products, Vernon,

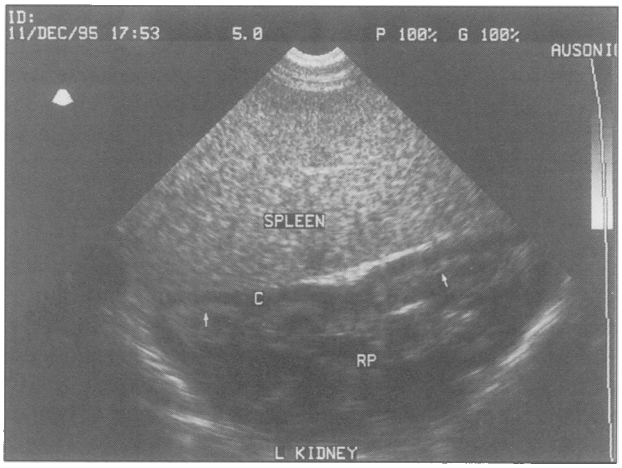

Figure 1. Longitudinal sonogram (5.0 MHz sector transducer) of the left kidney of a 10-year-old quarter horse with chronic phenylbutazone administration, demonstrating the highly echogenic renal medullary rim sign (arrows), relatively hypoechoic cortex (c), and renal pelvis (RP).

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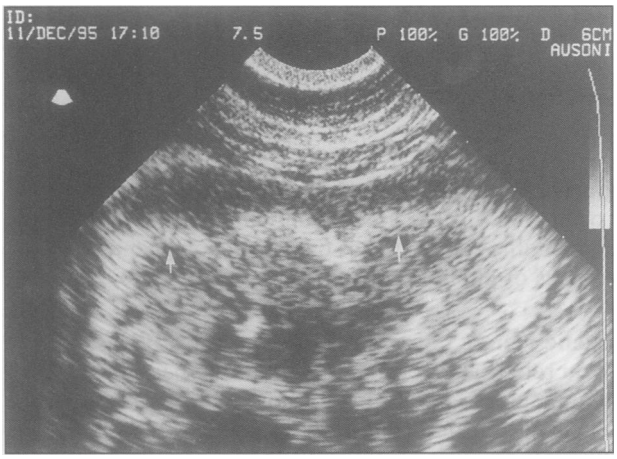

Figure 2. Longitudinal sonogram (7.5 MHz sector transducer) of the right kidney of a 10-year-old quarter horse with chronic phenylbutazone administration, demonstrating the medullary rim sign (arrows). Coarseness of the image is believed to be secondary to image magnification relative to transducer and/or monitor resolution.

California, USA) to the diet (113 g, PO, q24h), and to return for a check-up in 3 mo. Although the horse was never returned for reevaluation, follow-up via telephone 6 mo later determined that the gelding had gained his weight back and was doing well.

Case 2

A 4-year-old, 590-kilogram, quarter horse stallion was evaluated following the inadvertent administration of 4 doses of phenylbutazone (17 mg/kg body weight (BW), PO, q12h). Laboratory test results revealed leukopenia (3.5×10^9 cells/L; reference range: $5.5–12.5 \times 10^9$ cells/L), hypoalbuminemia (23 g/L; reference range: 30–41 g/L), hypoproteinemia (45 g/L; reference range: 60–80 g/L), and azotemia (creatinine 290 μmol/L; reference range: 110–250 μmol/L). Results of abdominal fluid analysis, urinalysis, uGGT to uCR ratio, and urinary fractional excretion of electrolytes were within normal values. Mild superficial erosions were noted on the nonglandular portion of the stomach during gastroscopic examination. Hyperechoic renal medullary rims were seen ultrasonographically in both kidneys, similar to those observed in Case 1. No other renal abnormalities were noted. Because of the hypoalbuminemia and hypoproteinemia, a provisional diagnosis of right dorsal colitis secondary to the administration of phenylbutazone was made. The administered phenylbutazone was also suspected in this case as the cause of the MRS. To relieve the azotemia, diuresis with polyionic fluids (100 mL/kg BW/24 h, IV) was initiated following sonographic evaluation. Fluid therapy was discontinued after repeat blood analysis revealed resolution of the azotemia. The stallion was discharged with instructions to discontinue all grass hay and grain and to introduce a complete pelleted diet. Dietary management included the addition of pysillium mucilloid (113 g, PO, q24h). The stallion was reevaluated 3 mo later. Laboratory data revealed normal renal parameters and increasing serum protein (58 g/L) and albumin (24 g/L) concentrations. Renal ultrasonography was also performed, to evaluate persistence of the MRS. Although less apparent than previously noted, the MRS was still observed. The stallion was evaluated again 6 mo after discharge. Laboratory data revealed normal serum protein (64 g/L) and albumin (33 g/L) concentrations. Renal ultrasonography revealed presence of MRS. Again, it was less apparent than at the previous examination.

The medullary rim sign has been reported previously in humans (1) and small animals (2). Documented causes in dogs and cats include acute tubular necrosis as a result of toxic agents such as ethylene glycol; pyogranulomatous vasculitis secondary to feline infectious peritonitis, chronic interstitial nephritis (2,3), hypercalcemic nephropathy (4), and ibuprofen intoxication (unpublished observations). A less echogenic band, attributed to calcium deposition, has also been noted in clinically normal cats (2,5,6).

The distinct hyperechoic band within the medulla, at the corticomedullary junction, in these 2 patients was similar to the renal ultrasonographic findings described in an experimental study in neonatal foals administered high doses (5.0 mg/kg BW, PO, q12h, 7 d) of phenylbutazone (7).

In an experimental study (8) and in naturally occurring cases of ethylene glycol toxicity in dogs and cats (9), a "halo sign" has been described. The "halo sign" is hypoechoic tissue (normoechoic renal medulla) that is present between the hyperechoic cortex and hyperechoic medullary rim (2,3). In small animal ultrasonography, presence of the "halo sign" and hyperechoic medullary band is necessary for true and accurate diagnosis of a renal MRS (Biller DS, personal communication, 1996). No evidence of a "halo sign" was present in the experimental foals (7) or in our 2 cases. Possible explanations for the absence of a recognizable "halo sign" in horses are that the distance from the transducer to the kidney is much greater in horses and that the lower transducer frequency necessary to examine the kidney has diminished resolution, or that equine kidneys respond differently than those of small animals, presenting a slightly different sonographic image of renal medullary rims. Therefore, the hypoechoic tissue between the hyperechoic rim and cortex may not be present or apparent.

Medullary rim sign is thought to result from dystrophic calcification of the outer zone of the medulla, parallel to the corticomedullary junction, following renal damage (2,7). The outer zone of the medulla is reportedly the most metabolically active area of the medulla and, therefore, very sensitive to renal insult (2). Similar calcium deposits may form to a lesser extent in basement membranes of the cortical tubules and glomeruli (3,4). Acoustic shadowing of the medullary rim has not been reported, possibly because the calcification is microscopic (3,4,7).

Medullary rim sign has been reported as being an indicator of poor prognosis in dogs and cats when due to oxalate nephrosis or hypercalcemia secondary to paraneoplastic syndrome (3,4). However, MRS may not always indicate a poor prognosis, as it has been observed in normal cats (2,6). Additionally, in humans, MRS proved nonspecific and showed poor correlation with the severity of renal function and disease. Although the prognostic significance of MRS in the horse has

not been established, follow-up on Case 1 (via telephone) and Case 2 (reexamination) 6 mo after discharge found that both patients were doing well. However, as noted in both patients reported herein and as reported in neonatal foals, dogs, and most normal cats, the presence of an MRS suggests previous or ongoing renal damage (2,3,7).

Repeat renal ultrasonography in Case 2 performed 3 and 6 mo later, revealed that the MRS was still present, although less apparent. In one study involving humans with various forms of renal disease, no change in appearance of the MRS was demonstrated during recheck examination 6 mo to 5.5 y after the initial examination (1). Therefore, MRS may become less apparent over time, but may also persist indefinitely.

Phenylbutazone is a common NSAID administered to horses for the treatment of musculoskeletal disorders and is considered safe at recommended doses. The maximal recommended daily dose is 4.4 mg/kg BW (10). Administration of high doses may cause gastric ulceration, renal tubular cell and medullary crest necrosis, and right dorsal colitis (10). Phenylbutazone inhibits cyclooxygenase, an enzyme necessary for prostaglandin synthesis. Although prostaglandins are involved in the inflammatory response, they are necessary for regulation of normal blood flow to the kidneys and other organs, such as the gastrointestinal tract mucosa. Thus, the antiprostaglandin effects of phenylbutazone may cause small vessel constriction in the kidneys and gastrointestinal tract, leading to ischemia and necrosis (10).

The 2 cases reported herein demonstrate identical MRS. To date, this ultrasonographic change has only been documented secondary to phenylbutazone intoxication in neonatal foals (7). Of the horses reported herein, one had a history of chronic administration of phenylbutazone, while the other suffered an acute high dose administration. Although the significance of MRS is not yet known, the value of sonographic recognition of MRS may be for those patients in which MRS is an incidental finding, in horses presented with clinical signs, such as weight loss or anorexia, that are being administered phenylbutazone (and it is not known whether phenylbutazone is contributing to the problem), or in a case of acute overdose of phenylbutazone. In either instance, this should alert the clinician to question the owners further concerning previous or historical phenylbutazone administration and to evaluate the kidneys carefully for presence of MRS. Additionally, this sonographic appearance should prompt blood analysis for phenylbutazone levels, as well as specific evaluation of renal function. CVJ

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