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The ultrasonographic appearance of renal medullary striations and their association with renal disease and renal histopathology in domestic cats

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Abstract

Medullary striations (MS) have been anecdotally observed on ultrasound of feline kidneys; however, their significance is unknown. Aims of this retrospective, case control, pilot study were to describe the appearance, prevalence, and clinicopathological correlates of MS in a referral feline population. Still images from 1247 feline abdominal ultrasound studies performed between 2011 and 2021 were reviewed. Cats with MS were identified and compared with age-matched controls. Serum urea, creatinine, calcium, phosphate, and calcium-phosphate-product, plus urine specific gravity, urine protein: creatinine ratio (UPC), prevalence of active sediment (defined as > 5 red (RBC) or white blood cells (WBC) per high-power field) and prevalence of positive urine culture were compared between MS and control groups using the Mann–Whitney *U* test or Fisher's Exact test. Data are presented as median [range]. 27 cats were identified as having MS, giving a prevalence of 2.2% with a significantly higher proportion being seen in males ($P = 0.018$). Medullary striation cats had significantly higher UPC values than controls (0.46 [0.16–7.57] vs. 0.16 [0.07–2.27]; $P = 0.006$). Cats with MS were more likely to have active urinary sediments (39% vs 8%, $P = 0.023$), but no difference in prevalence of positive urinary cultures was observed between groups. There was no significant difference in other parameters between MS and control cats. Renal histopathology performed in three MS cats revealed focal regions of linear medullary fibrosis. Medullary striations are associated with proteinuria and urinary tract inflammation in cats, which may reflect renal tubular dysfunction and/or inflammation. Hence identification might allow for earlier detection of renal pathology.

KEYWORDS

active urinary sediment, feline, kidney, medullary fibrosis, proteinuria

Abbreviations: KD, kidney disease; MRS, medullary rim sign; MS, medullary striations; UPC, urine protein: creatinine ratio; US, ultrasonography/ultrasound.

1 | INTRODUCTION

The ultrasound (US) appearance of the kidney in cats has been widely described in the literature with some features considered to be within normal limits for some when considering factors such as breed, age, sex, neutering status, and body weight.[1–4] The renal medulla, which surrounds the renal pelvis, has a known typical appearance on US; it is hypoechoic to anechoic when compared to the renal cortex and is divided into lobules by linear echogenicities that represent borders of the interlobar arteries and diverticuli.[1–5] Variations to the appearance of the outer renal medulla on US have been reported, with some changes known to have important diagnostic implications in both cats and dogs. A hyperechoic band paralleling the corticomedullary junction known as the medullary rim sign (MRS), have been widely described in cats and dogs with and without kidney disease (KD).[1,3,5,6–14] A hypoechoic band (halo sign) described in cases of ethylene glycol toxicity[9,15] and, radiating hyperechoic bands affecting both the cortex and medulla have been reported in cats with chronic end-stage KD.[1,16]

Medullary striations (MS) have been anecdotally observed on ultrasound examinations of feline kidneys; however, their significance is unknown. Medullary striations appear as distinctive hyperechoic linear streaks that radiate from the corticomedullary junction and traverse the outer to inner medulla and do not affect the renal cortex. There are multiple reports of hyperechoic, irregular MS in the outer renal pyramids of neonates, children, and adults in the literature, that are associated with some forms of autosomal recessive and dominant polycystic KD,[17,18] and medullary sponge KD.[19] Similar US findings have also been reported in cases of nephrocalcinosis with hypercalcemia in humans.[20,21] However, to date, no published study in veterinary medicine has described what we propose as MS in the medulla of feline kidneys and whether their identification has diagnostic value in this species.

Our objectives of this present pilot study were to (1) describe the appearance and prevalence of MS in a referral population of feline patients undergoing US examination, (2) determine if the appearance of MS has any clinicopathological correlates by comparing with an age-matched control population, and (3) to describe renal histopathological findings in cats that have MS identified on US. We hypothesised that the US appearance of MS would be due to medullary fibrosis.

2 | METHODS

2.1 | Selection and description of study subjects

This retrospective case-control study was conducted under approval of the Ethics and Welfare Committee (approval No. CR546) of the Department of Veterinary Medicine, University of Cambridge, UK. The hospital Picture Archiving and Communication System (PACS) was examined for all cats that had an abdominal US performed between January 2011 and June 2021, by either an ECVDI-certified radiologist or a radiology resident-in-training under direct supervision by a boarded radiologist. The still images of the kidneys were retrospectively reviewed by a diagnostic imaging intern with over 9 years of experience performing kidney ultrasound examinations (CB) and a final year veterinary student (WSL) who at the time were all blinded to the cats' presenting signs and any laboratory data obtained at the time US examination was performed.

2.1.1 | Study group

Cats were included in the MS group if they had MS identified on US still images, in either one or both kidneys. Similarly, cats were excluded from the study if there were incomplete images of kidneys or renal parenchymal changes preventing visualisation of the MS, or if urinary tract obstruction was present, and finally if there were no contemporaneous renal laboratory data available.

2.1.2 | Control group

The control group was selected by reviewing the PACS still US images of cats age-matched to the MS group who had normal kidneys on ultrasound. Inclusion criteria were normal renal length (range 3.0–5.3 cm),[1–5] good corticomedullary definition with a smooth renal outline, and no renal pelvis dilation. Increased cortical echogenicity in male neutered cats was considered a normal variant.[1,3,5,13,22] Similar exclusion criteria outlined for the study group were applied.

2.2 | Data recording and analysis

2.2.1 | Ultrasound image and patient data recording

Kidney US images of the pre-selected cats for the MS and control groups were then subsequently randomly and blindly reviewed by one ECVDI-certified radiologist (MAG) who was unaware of their group designation for consensus opinion. Ultrasound data extracted from the still image review of all MS cats included renal length (longitudinal plane measurement in cm) taken directly from the caliper points pre-recorded on the still images, renal outline (smoothly marginated versus irregular), renal cortical echogenicity (normal, increased or reduced) including the presence of any parenchymal changes (bands/cysts/nodules/masses), corticomedullary definition (normal, increased or reduced), appearance of the medulla echogenicity (normal, increased, MRS, halo sign, bands or MS) or any renal pelvis dilation (subjective assessment made as not all renal pelvis dimensions were recorded). A brief description of the US appearance of the urinary bladder was also made based on wall thickness (thin or thick), appearance of urinary bladder wall epithelial lining (smooth, irregular, or mass lesion), and luminal contents (anechoic, sediment, calculi, or speckles). For all selected cats, medical records were searched for signalment (breed, age, sex, neutering status, and body weight) and contemporaneous renal laboratory data (serum concentrations of urea, creatinine, phosphorus, total calcium, electrolytes, and urinalysis data). Renal laboratory data were determined from blood samples collected on the same day US examination was performed. Active sediment was defined as WBC or RBC > 5 cells per high-power field on urine sediment microscopy.

2.2.2 | Histological analysis

The pathology database was then searched for all cats included within the MS and control groups that underwent full post-mortem examination. Renal cortical biopsy samples were excluded as the purpose of this study was to histologically assess the renal medulla. Cats that had renal tissue stored were then reviewed by one author (FCC), a boarded and RCVS-recognised Specialist in Veterinary Pathology (Small Domestic Animals), who was aware of the sample's group designation and given the prerequisite to scrutinise the renal medulla to fulfill the objectives of this study. Histological analyses were performed on two formalin-fixed, paraffin-embedded kidney samples. Three μm sections were stained with hematoxylin and eosin, and Masson's trichrome stains. Each kidney was considered an independent sample, with a brief histological description and morphological diagnoses made for each submitted sample.

2.3 | Statistical analysis

Selection and completion of statistical tests were performed by one observer (TW), a boarded veterinary clinical pathologist with over 10 years experience of statistical analysis. Statistical analyses were performed using commercially available software (IBM®SPSS Statistics, Version 27.0 (IBM, New York, USA)). All continuous variables are presented as median [range]. Comparisons of continuous variables including renal biochemical parameters, USG, and UPC between groups were performed using the Mann-Whitney U test. The prevalence of males (vs. females), active sediment, and positive urine culture was compared between the MS and control groups using the Fisher's exact test. No statistical analyses were performed on the histological data, with this data being purely descriptive in nature. A *P*-value of < .05 was considered statistically significant.

3 | RESULTS

In total 1247 feline abdominal ultrasound studies were reviewed on the PACS system using DICOM viewer (Visbion, Surrey, UK). Twenty-seven cats were identified as having MS (23 neutered males and 4 neutered females) (Figure 1B). The prevalence of MS in our population was 2.2% (95% confidence interval [CI] 1.4-3.1%). The MS group included 13 domestic shorthairs, 4 domestic longhairs, 3 Siamese, 3 Ragdolls, 1 Abyssinian, 1 Birman, 1 Bengal, and 1 Persian. Cats were 9 [4–14] years old with a bodyweight of 4.5 [2.5–7.1] kg. The same number of aged-matched cats (n = 27) who fulfilled the inclusion criteria were enrolled into the control group (1 entire male, 13 neutered males, and 13 neutered females) (Figure 1A). The control group included 15 domestic shorthairs, 3 domestic longhairs, 1 Abyssinian, 3 Bengals, 1 Siamese, 1 Persian, 1 Ragdoll, 1 British shorthair and 1 Turkish van. Cats in the control group were 9 [3—14] years old with a body weight of 4.3 [2.3–6.6] kg. When comparing the signalment of cats in each group there were significantly a higher proportion of males in the MS group compared to the control group ($P = 0.018$).

3.1 | Ultrasound findings

Ultrasound examinations were performed using varying US machines (LOGIQ E9, GE Healthcare Medical Systems, Chicago, USA; ATL HDI 5000, Philips Medical Systems, Amsterdam, Netherlands; EPIQ 7G, Philips Medical Systems, Amsterdam, Netherlands). Both multi-frequency microconvex 3–10 MHz (C3-10, GE Healthcare Medical Systems, Chicago, USA); 8-5 MHz (C8-5, Philips Medical Systems, Amsterdam, Netherlands) and linear 12–5 MHz (L12-5, Philips Medical Systems, Amsterdam, Netherlands); 18-5 MHz (L18-15, Philips Medical Systems, Amsterdam, Netherlands) transducers were used for US examination as per institutional protocol. Longitudinal and transverse images of each kidney for each study participant were available for review.

In just over a half of the cats (52%; 95% CI 32–71%) MS was seen bilaterally. Unilateral MS was identified in the left kidney of 10 of 27 (37%; 95% CI 19–58%) cats (Figure 1B) and in the right kidney in three of 27 (11%; 95% CI 2–29%). Kidneys in which MS were identified were symmetrical in size and within the accepted normal size range for cats (left kidney 4.09 cm [3.25–5.11 cm] and right kidney 4.39 cm [3.13–5.61 cm]). In 23 of 27 (85%; 95% CI 66–96%) cats, a smooth renal outline was seen and in 22/27 (81%; 95% CI 62–94%) good corticomedullary definition was observed. An MRS was identified in 8/27 (30%; 95% CI 14–50%) of cats and cortical banding was only identified in 5/27 (19%; 95% CI 6–38%) of cats with MS. Table 1 lists all the US features observed in cats with MS identified in their kidneys.

3.2 | Laboratory findings

Selected clinicopathological data are outlined in Table 2. There was no significant difference in serum concentrations of urea, creatinine, phosphate, total calcium, or calcium-phosphate product or USG between cats with and without MS. However, UPC was higher in cats with MS compared to the control group (0.46 [0.14–7.57] vs. 0.16 [0.07–2.27]; $P = 0.006$) (Figure 2). Cats in the MS group had a significantly greater prevalence of active urinary sediment compared to control cats (39% vs. 8%; $P = 0.023$, Table 2) however there was no difference in the proportion of cats with positive urine culture between the groups ($P = 0.206$, Table 2). When cats with active urinary sediment and positive urine cultures were excluded, UPC was still significantly higher in MS cats compared to the control group (0.43 [0.16–7.57] vs. 0.15 [0.07–1.09] $P = 0.005$).

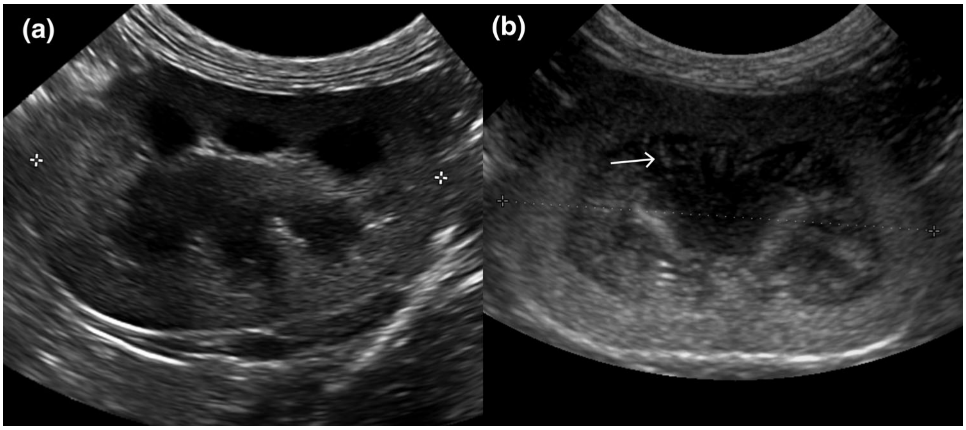

FIGURE 1 Representative ultrasonographic images from two cats included in the study showing normal kidney and kidney with medullary striations (MS). A, Longitudinal B-mode image of normal left kidney of a cat (renal length 3.16 cm between calliper points). B, Longitudinal B-mode image of left kidney with MS (renal length 3.8 cm between calliper points). MS is characterised by hyperechoic linear striations in the outer medulla radiating into the inner medulla (white arrow). The increased cortical echogenicity seen only in the far field in this example was assumed to be an artifact. Images (A-B) have both been obtained using a multifrequency microconvex 8-5 MHz (C8-5, Philips Medical Systems, Amsterdam, Netherlands) transducer

TABLE 1 Prevalence of renal ultrasonographic findings in cats within the medullary striation study group

Ultrasonographic finding	MS group (n = 27)
Bilateral medullary striations (yes)	14/27 (51.9%)
Left unilateral medullary striations (yes)	10/27 (37%)
Right unilateral medullary striations (yes)	3/27 (11.1%)
Smooth renal outline (yes)	23/27 (85%)
Irregular renal outline (yes)	4/27 (15%)
Hyperechoic cortices (yes)	8/27 (30%)
Good corticomedullary definition (yes)	22/27 (81%)
Poor corticomedullary definition (yes)	5/27 (19%)
Medullary rim sign (yes)	8/27 (30%)
Cortex bands (yes)	5/27 (18.5%)
Medullary bands (yes)	0/27 (0%)
Renal pelvis distension (yes)	3/27 (11%)
Mineral foci	0/27 (0%)
Cortical cysts	1/27 (4%)
Renal infarcts	1/27 (4%)
Mass lesion	1/27 (4%)
Nephroliths	1/27 (4%)
Altered perirenal tissue	1/27 (4%)

Note: Data are reported at median and range (minimum-maximum) or frequency and percentage of total cases. MS, medullary striations.

3.3 | Histology findings

Four cats in the MS group underwent full postmortem examination, however stored renal samples were only available for three cats. In all three cases, there was mild to moderate increased collagen deposition (fibrosis) present focally within the medullary interstitium observed in a “linear pattern” (Figure 3) and multifocal small aggregates of lymphocytes within the cortical interstitium. In one of the samples, additional plasma cells were also seen in the cortical interstitium, and in another there was also evidence of scattered mineralisation of the cortical tubule lumen. The histological diagnoses for all three cases were very similar; chronic lymphocytic (lymphoplasmacytic in one case) interstitial nephritis, mild to moderate in two of three cases and moderate to severe in

TABLE 2 Selected laboratory data comparing cats with medullary striations to a control group

Parameter	MS group (n = 27) median (range)	Control group (n = 27) median (range)	*P*-value
Urea (5.4-10.7 mmol/L)	7.9 (5.2-31.3)	8.7 (4.6-17.1)	0.812
Creatinine (56-153 μmol/L)	107 (68-326)	117 (65-263)	0.464
Phosphate (0.9-2.1 mmol/L)	1.46 (1.0-1.83)	1.31 (0.47-1.83)	0.742
Calcium (2.0-2.7 mmol/L)	2.36 (1.9-2.56)	2.35 (1.92-3.19)	0.660
Ca x Pi product	3.35	3.09	0.431
USG	1.038 (1.010-1.050)	1.044 (1.018-1.050)	0.314
UPC	0.46 (0.16-7.57)	0.16 (0.07-2.27)	*0.006**
Urine active sediment[a]	7/18 (39%; 95% CI 17–64%)	2/29 (8%; 95% CI 1–23%)	*0.023**
Urine positive culture	0/9 (0%; 95% CI 0–33%)	2/8 (25%; 95% CI 3–65%)	0.206

Notes: Reference intervals are listed after each laboratory parameter. **P* value of < 0.05 is considered significant. A Mann-Whitney U test was used to compare urea, creatinine, phosphorus, calcium, Ca x Pi, USG and UPC ration between the groups. A Fisher's exact test was used to compare the prevalence of urinary active sediment and positive culture between groups. Ca x Pi, calcium phosphate product; MS, medullary striations; UPC, urine protein creatinine ratio; USG, urine specific gravity. CI, confidence interval.

[a]Urine active sediment defined as white or red blood cells > 5 cells per high power field on microscopy.

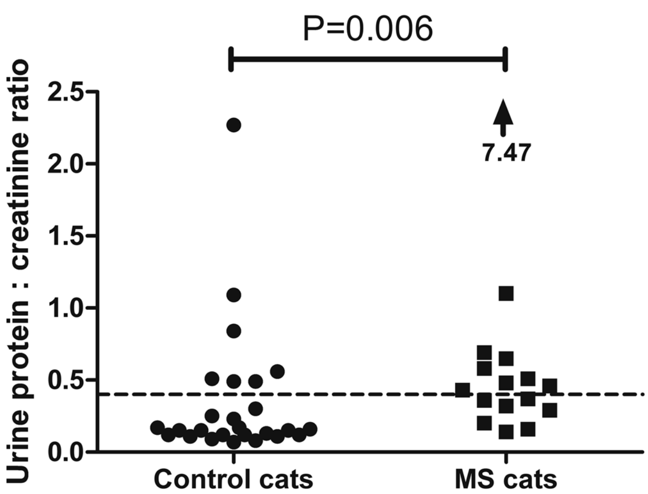

FIGURE 2 Scatter plot showing the individual urine protein creatine ratios (UPC) of each of the 27 cats in the control (black circle) and medullary striation (black square) groups. Black arrow indicating higher UPC seen in study group outside of the *y*-axis. Medullary striation cats had significantly higher UPC values than controls ($P = 0.006$). The dashed line (- - -) represents the recommended treatment threshold of 0.4 for persistent proteinuria. MS, medullary striations

one of three cases with chronic focal mild to moderate medullary fibrosis.

One cat within the control group underwent post-mortem examination and renal tissue was available for review. This sample demonstrated moderate numbers of lymphocytes within the cortical interstitium (lymphocytic interstitial nephritis), multifocal proliferative glomerulonephritis, and with multifocal regions of cortical interstitial fibrosis only.

4 | DISCUSSION

In this retrospective, case control pilot study, we describe the US appearance of previously unreported MS in a small population of cats. The authors hypothesised that the US appearance of MS would be due to medullary fibrosis and histopathology data obtained from this study does suggest that fibrosis is the likely cause. The prevalence of MS in our population was 2.2%, and although this is a low prevalence it is not a negligible percentage. The current study population is limited to a single referral hospital population, so the true prevalence of MS within the general feline population remains unknown. Evaluation of specific features of the study group revealed that cats with MS tend to be male but with no clear breed predilection. Over half of the cats had MS bilaterally with unilateral right kidney involvement being less common. Renal length was normal in affected cats, with length ranges of 3.1–5.6 cm that correlates well with other studies.[3,5,6] Over 80% of the kidneys with MS in our study had a smooth renal outline and good corticomedullary definition with an MRS also identified in approximately 30% of cats with MS. The prevalence of MRS in our cat population too was very similar to previous studies,[8,13] which could suggest that the prevalence of MS identified in our study maybe representative of the wider cat population and hence MS is not a common finding.

Our study demonstrated no significant difference in renal parameters and markers of calcium-phosphate metabolism (urea, creatinine, phosphate, calcium, and USG) between the MS group and the control group. However, this study has identified that cats with MS had significantly higher UPC and a greater prevalence of active sediment when compared to the control group. All urine samples in the study were collected by cystocentesis, excluding urogenital contamination, and given that all cats in the study had normal plasma protein levels and negative urinary cultures, suggests either sterile urinary tract inflammation or primary renal proteinuria as a cause to the higher UPC.[23] A caveat to this is the influence of hematuria on UPC. A previous study has looked at the effect of blood contamination on UPC in both cats and

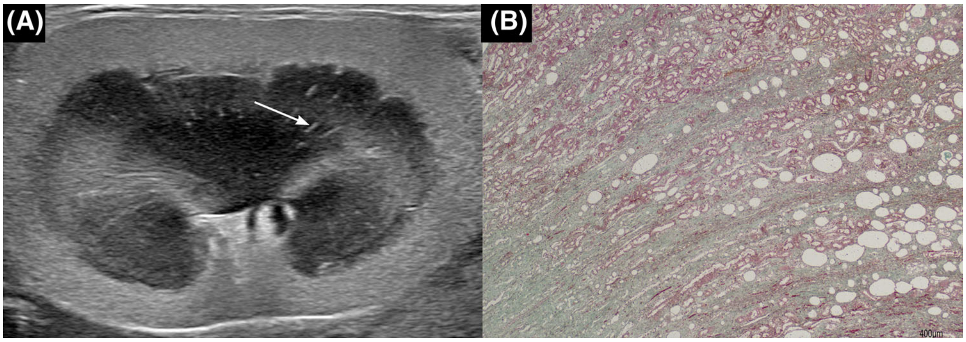

FIGURE 3 Representative ultrasonographic and histopathological image of one of the cats in the medullary striation group highlighting the linear fibrosis of the medullary interstitium. A, Longitudinal B-mode image of right kidney with medullary striations (white arrow) with a hyperechoic renal cortex obtained using a multifrequency linear 18-5 MHz (L18-15, Philips Medical Systems, Amsterdam, Netherlands) transducer. B, Masson's trichrome staining, magnification ×100 [Color figure can be viewed at wileyonlinelibrary.com]

dogs which suggests that microscopic haematuria (≥250 RBC/hpf) can increase UPC values.[24] Some cats in both of our study groups did have evidence of microscopic hematuria on urinalysis (assumed iatrogenic due to cystocentesis), however all had much lower numbers of RBC seen microscopically, suggesting this is an unlikely cause of the higher UPC found in this study. Interestingly, if all cats within the study with active sediment (WBC or RBC > 5 cells/hpf) and positive urine culture were excluded, MS cats still had significantly higher ($P = 0.005$) UPC that suggests that the differences in UPC are not just down to urinary tract inflammation or the possible effects hematuria and perhaps do reflect tubular dysfunction and primary renal proteinuria.

Identification of proteinuria is important for many reasons. First, persistent renal proteinuria indicates renal tubular dysfunction regardless of the serum creatinine concentration.[25–28] A previous study evaluated predictors of azotemia in cats, and identified proteinuria as being associated with the subsequent development of azotemia in this species.[25] Similarly, proteinuria is also negatively associated with survival time in cats with chronic KD.[26] The current IRIS[29] and ACVIM guidelines[23] both suggest antiproteinuric therapy should be instituted in cats with chronic KD and persistent proteinuria (UPC > 0.4). Considering that the median UPC in our MS group was 0.46, evaluation of UPC in cats with MS identified on US may be warranted since these cats may be more likely to be proteinuric. Our current study design was not intended to investigate the longer-term follow-up of cats with MS and so demonstration of persistent proteinuria or monitoring for the subsequent development of azotemia in MS cats was not evaluated in this study, but this would be worthy of further investigation.

Regarding the US appearance of renal tissue, previous studies have suggested that differences in the acoustic impedance of medullary tissue maybe due to regional intraluminal mineralisation within renal tubules, fibrosis, lipid deposition, or crystallisation in patients without KD.[1,3,5,8,9,13,28,30] Physiologically the renal medulla is relatively more hypoxic when compared to the renal cortex, with the medulla receiving only 10% of cortical blood flow. Tubulointerstitial hypoxia is known to stimulate the production of collagen and smooth muscle actin, resulting in increased fibrogenesis, which supports our hypothesis that fibrosis was the likely cause of MS.[31] There is a known link between progressive renal fibrosis and KD in both humans and cats,[28,32] the mechanisms behind which are incompletely understood, however certain factors, such as proteinuria have been implicated in fibrosis progression.[23,25,26,28,29] Histopathology performed on three MS cats confirmed the presence of increased collagen deposition (fibrosis) present focally within the medullary interstitium, organised in a "linear pattern" and was not observed in the one control sample reviewed. In absence of medullary mineralisation as seen in humans with hyperechoic MS which are thought to represent a linear pattern of calcium deposition[17,18] or lipid deposition being identified in the samples analysed, fibrosis is the only remaining tissue type that could account of the echogenic appearance of MS on US. This suggests that fibrosis is the likely cause of the hyperechoic linear striations identified in the medulla on US in all MS study group cats. However, the small sample of cats having histopathology performed in this study does limit conclusions about definitive histopathologic corroboration being drawn.

When considering the findings of this study, it is important to be aware of the study limitations. This was a retrospective study with a small sample size and not all the study group cats had corroborating histopathology performed. In our study, the acquisition of US images of the kidneys was obtained by multiple radiologists over the study period using various machines with both convex (3-10, 8-5 MHz) and linear (12-5, 18-5 MHz) transducers being used. The type of transducer employed can affect renal echogenicity and hence may have induced some bias into the study data.[9,13,15] In addition to this, the retrospective nature of our study only allowed for review of static ultrasound images and may have hindered image interpretation. Not all cats within the current study had full urinalysis, including urine culture, and given the association of MS with proteinuria this may influence how the UPC results are interpreted. Lastly, multivariable analysis was not performed and so meaningful correlations between all variables (sex, UPC and active sediment) could not be determined in this study.

In conclusion, this study has found that cats identified with MS on US examination tend to be male and are more likely to be proteinuric and likely represent focal regions of medullary fibrosis. Documentation of MS may therefore reflect the early presence of chronic KD, and further testing of renal function (serum creatinine, urine specific gravity) and IRIS sub-staging (including evaluation of UPC) may be warranted in these cats.

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LIST OF AUTHOR CONTRIBUTIONS

Category 1

(a) Conception and Design: Bentley, Genain, Williams
(b) Acquisition of Data: Bentley, Constantino-Casas
(c) Analysis and Interpretation: Bentley, Williams

Category 2

(a) Drafting the Article: Bentley
(b) Revising Article for Intellectual Content: Bentley, Genain, Williams, Constantino-Casas

Category 3

(a) Final Approval of the Completed Article: Bentley, Genain, Williams, Constantino-Casas

Category 4

(a) Agreement to be accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Bentley, Williams, Genain, Constantino-Casas

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

PREVIOUS PRESENTATION OR PUBLICATION DISCLOSURE

This manuscript has not been published elsewhere and is not under consideration by any other journal. An abstract has been submitted and presented at BSAVA congress 2022 UK.

EQUATOR NETWORK DISCLOSURE

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