Cystine and urate cystoliths in dogs are frequently visible on radiographs prior to surgical or nonsurgical removal

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OBJECTIVE
To investigate the frequency at which cystine and urate cystoliths (stones) are visible on radiographs prior to surgical or nonsurgical retrieval.

METHODS
Records of client-owned dogs (n = 331) were analyzed between January 2019 and December 2023 for cystoliths submitted for stone analysis after surgical removal or nonsurgical retrieval. Records were analyzed for cystolith type; when cystine or urate stones were identified, records were analyzed for signalment, procedure, presence of mineral opaque cystoliths on pre-procedural radiographs, urine pH and crystalluria, history of previous cystoliths, prior prescription diet attempt, recurrence, and genetic, congenital and acquired comorbidities. Descriptive statistics were generated after data collection.

RESULTS
31 of 331 (9%) were cystine stones, 49 of 331 (15%) were urate, and 1 of 331 (0.3%) was a mix of urate and cystine. When radiographs were taken prior to stone removal, 24 of 28 (85%) of urate, 24 of 26 (92%) of cystine, and 1 of 1 (100%) of urate/cystine were visible on radiographs.

CONCLUSIONS
Cystine and urate stones are visible on survey radiography at a high frequency in dogs.

CLINICAL RELEVANCE
While cystine and urate stones have been historically designated as radiolucent, they are frequently radiopaque on radiographs. Radiopacity is commonly used as one of the criterion to determine whether a dissolution or prevention diet is an appropriate management technique, particularly when determination of the stone type has yet to be performed. As a result, these findings may prompt clinicians to investigate other patient-specific factors before a specific dietary recommendation is made.

Keywords: cystoliths, soft tissue surgery, cystine, urate, digital radiography

Prevalence of stones removed and submitted for analysis has been previously documented: Calcium oxalate stones (calcium oxalate monohydrate and dihydrate) account for 42.8% of stones removed from dogs, while struvite stones account for 36.8%. These, along with silica (0.4%), calcium phosphate carbonate (0.5%), brushite (0.3%), calcium phosphate apatite (0.1%), and mixes of these stone types are considered to be moderately to markedly radiopaque. Cystine (2.1%), urate salts (4.0%), and xanthine stones (0.1%) are considered to be radiolucent to marginally radiopaque. Cystine stones are most commonly found in male dogs (97.2%), and English Bulldogs, mixed-breed dogs, Chihuahuas, Dachshunds, French Bulldogs, and Pitbulls account for breeds with the highest prevalence. Urine pH upon diagnosis of cystine stones has shown to be less than or equal to 6.5. Genetic predisposition has been described and genetic
tests are available for cystinuria-associated markers types 1 through 3. Urate stones are more common in males (79%), but may be found in females up to 19% of the time. Urate stones are most commonly found in Dalmatians, due to their genetic predisposition and in dogs with portosystemic shunts (extrahepatic, intrahepatic, or multiple acquired shunts). Urine pH upon diagnosis of urate stones has shown to be less than or equal to 6.5. Of those stone types mentioned above, only struvite stones may be dissolved alone by diet. Urate and cystine stones may, in part, be prevented by diet; however, the selection of a commercial dissolution diet for struvite stones varies from commercial cystine/urate prevention diets.

As previously stated, cystine and urate stones have previously been designated as radiolucent or marginally radiopaque. In human literature, these stones carry the same designation or are considered poorly visible on radiographs. The frequency at which false negatives occur in the radiographic diagnosis of stones, based on the stone type, has been published in veterinary literature. False negatives occur in 20% to 25% of cases in which cystine and urate stones are present, while they occur in 1.7% to 5% of cases in which calcium oxalate or silica stones are present. A recent case series, however, reported 2 cases in which 100% cystine and urate stones were clearly visible on survey radiography and therefore may suggest these stones are more commonly diagnosed on survey radiography than previously thought. Additionally, a recent in vitro study noted that cystine and urate uroliths placed in a urinary bladder phantom to mimic the canine abdomen had a sensitivity of 96.7% and 97.7% respectively, and 100% specificity each for digital radiography.

The aim of this study was to determine the frequency at which 100% urate and cystine stones were visible on survey radiography before their removal via surgical or nonsurgical methods in dogs. Our hypothesis was that both cystine and urate stones would be visible on pre-procedural radiographs much more frequently than previously reported.

Methods

Data collection

Medical records of dogs presenting to the University of Florida Small Animal Hospital between January 2019 and December 2023, whose stones were submitted for analysis after removal via surgery, laser lithotripsy, or basket cystoscopy, were reviewed. The subjects were divided into 2 groups, on the basis of stone analysis reports, as those with cystine or urate stones (100% cystine, 100% urate, mix of cystine and urate) and those with classically radiopaque stones (100% calcium oxalate – monohydrate or dihydrate or both, 100% struvite, 100% calcium phosphate carbonate, 100% brushite, 100% silica, 100% calcium phosphate apatite, or stones of mixed composition including or not including cystine and urate). Subjects were included in the cystine/urate group if their stones were either 100% urate or 100% cystine or a mix of only these 2 stone types. All stones submitted for stone analysis were sent to the Minnesota Urolith Center at the University of Minnesota. Within the cystine/urate group, signalement, procedure, stone analysis, crystalluria and bilirubinuria, history of previous stones and type, whether a dissolution or prevention diet had been previously attempted, whether record of recurrence occurred, time to recurrence and presence of genetic, congenital comorbidities and acquired comorbidities were documented. It was documented whether cystine and urate stones were visible on pre-procedural radiographs by veterinarians or radiologists in the medical record. Procedures were classified as surgical or nonsurgical, with surgical procedures including any procedure in which an incision was made into the bladder for the purpose of stone removal (cystotomy, percutaneous cystolithotomy, laparoscopic-assisted cystotomy). Nonsurgical procedures included urohydropulsion, laser lithotripsy, basket retrieval via cystoscopy or urethroscope, or a combination of these.

Statistical analysis

Frequencies and descriptive data were determined using Excel (version 16.37; Microsoft Corp).

Results

Three-hundred and thirty-one records of dogs that underwent surgical or nonsurgical removal for cystoliths were evaluated. Of the cases in which the stones that were submitted for stone analysis, 31 of 331 (9%) were cystine stones, 49 of 331 (15%) were urate stones and 1 of 331 (0.3%) were a mix of urate and cystine stones, while 250 of 331 (73%) were either calcium oxalate, struvite, calcium phosphate carbonate, silica, brushite, or a stone of mixed composition, including or not including cystine and urate.

Thirty-one dogs were diagnosed with 100% cystine stones. Of dogs with cystine stones, 4 of 31 (13%) were castrated males, while 27 of 31 (87%) were intact males. Eight of the 31 (28%) dogs diagnosed with cystine stones were mixed-breed dogs, while 6 of 31 (19%) were French Bulldogs, 4 of 31 (13%) were English Bulldogs, 2 of 31 (7%) were Miniature Schnauzers, 2 of 31 (6.5%) were Dachshunds, 2 of 31 (6%) were Chihuahuas, 2 of 31 (6.5%) were American Staffordshire Terriers, 1 of 31 (3%) was a Vizsla, 1 of 31 (3%) was a Basset Hound, 1 of 31 (3%) was a Yorkshire Terrier, and 1 of 31 (3%) was an Australian Shepherd. The average age of these dogs was 4.7 years. Congenital comorbidities were specified in 16 of 31 (52%), the most common of these was brachycephalic obstructive airway syndrome (BOAS) in 8 of 31 (26%). Benign prostatic hyperplasia was noted in 4 of 31 (13%). Two dogs were
tested for genetic cystinuria-associated markers; one dog was a type 2 heterozygote and one dog was negative for type 1, 2, and 3 cystine associated markers. Urinalysis was performed in 22 of 31 (71%) of dogs diagnosed with cystine stones prior to their removal. Cystinuria was identified on urinalysis in 10 of 22 (45%), struvite crystals were noted in 1 of 22 (4.5%), and struvite and cystine crystals were noted in 1 of 22 (4.5%). The average pH on urinalysis of dogs with cystine stones was 7.0 (range, 6-8). Three of 31 (10%) had a history of cystine stones, 1 of 31 (3%) had a history of urate stones, and 24 of 31 (77%) had no history of stones, while the history of 3 of 31 (10%) was not specified. Twenty-eight of 31 (90%) had no record of recurrence of cystine stones, while 2 of 31 (6%) had recurrence of stones at an average of 4 months after first stone removal (range, 1 – 6 months). One of the 2 males with recurrence of cystine stones was castrated. One dog with a prior history of cystine stones developed calcium oxalate stones 2 and a half years after cystine stone removal. Three of 31 (10%) had their stones retrieved via nonsurgical methods, while 28 of 31 (90%) had their stones removed surgically. Survey radiographs were taken in 26 of 31 (77%) cases prior to stone removal and when these radiographs were taken, cystine stones were visible in 24 of 26 (92%; Tables 1 and 2). In the 2 of 26 (8%) cases in which stones were not visible when radiographs were taken, abdominal ultrasound provided a confirmatory diagnosis. Common radiographic features (size and number) of the mineral opaque cystine stones are shown in Table 2. Eight of these 31 (26%) had been trialed on a commercial urinary diet before removal of their cystine stones. Two of 26 (8%) were trialed on a dissolution diet labeled for struvite stones, 4 (15%) on a cystine prevention diet, and 2 (25%) were on an unspecified dissolution diet. Three of 4 (75%) of the dogs on a diet labeled for the prevention of cystine stones had a history of stones. The 2 dogs that were trialed on a dissolution diet labeled for struvite stones had no prior history of stones.

Table 1—Method of diagnosis for urate and cystine cystoliths.

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Cystine</th>
<th>Urate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographs</td>
<td>24 (77.4%)</td>
<td>22 (45%)</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>5 (16%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>CT</td>
<td>0 (0%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.6%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

Forty-nine dogs were diagnosed with 100% urate stones. Of dogs with urate stones, 29 of 49 (59%) were castrated males, 16 of 49 (32%) were intact males, and 4 of 49 (8%) were spayed females. Thirteen of 49 (26%) were Dalmatians, 8 of 50 (16%) were mix breed dogs, 5 of 49 (10%) were Shih Tzus, 3 of 49 (6%) were Pugs, 3 of 49 (6%) were Yorkshire Terriers, 2 of 49 (4%) were Havanese, 2 of 49 (4%) were Cocker Spaniels, 2 of 49 (4%) were English Bulldogs, 2 of 49 (4%) were West Highland Terriers, 1 of 49 (2%) was a Maltese, 1 of 49 (2%) was a Beagle, 1 of 49 (2%) was a Miniature Schnauzer, and 1 of 49 (2%) was a Rhodesian Ridgeback. Thirty-six of 49 (73%) had urate stones removed surgically. Thirty-six of 49 (73%) had a prior history of urate stones, 10 of 49 (20%) had a history of a congenital portosystemic shunt, 20 of 49 (40%) had multiple acquired portosystemic shunts, or microvascular dysplasia. Thirty-six of 49 (73%) had urate stones removed surgically, whereas 13 of 49 (27%) had them removed via nonsurgical methods. In 28 of 49 cases (57%), radiographs were taken prior to stone removal. Urate stones were noted on radiographs in 24 of 28 (85%) of these cases (Tables 1 and 2). In 4 of 28 (14%), urate stones were not visible on abdominal radiographs, but were identified on abdominal ultrasound or cystourethrogram. Common radiographic features of the mineral opaque urate stones (size and number) are shown in Table 2. Five of 49 (10%) had been trialed on a urate stone prevention diet prior to stone removal. All of these dogs had a prior history of urate stones.

Table 2—Radiographic features of cystine and urate cystoliths on pre-procedural radiographs.

<table>
<thead>
<tr>
<th>Stone type</th>
<th>Subjects with pre-procedural radiographs</th>
<th>Subjects with mineral opaque stones</th>
<th>Diametera</th>
<th>No. of stones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystine</td>
<td>26</td>
<td>24 (92%)</td>
<td>&lt; 0.5–17.3 mm</td>
<td>Few (≤ 10) 8 (33.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 1–10 mm</td>
<td>Multiple (11–20) 8 (33.3%)</td>
</tr>
<tr>
<td>Urate</td>
<td>28</td>
<td>24 (85%)</td>
<td></td>
<td>Few (≤ 10) 12 (42%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple (11–20) 4 (16%)</td>
</tr>
</tbody>
</table>

aData are reported as range.
One dog was diagnosed with stones of mixed composition containing only urate and cystine. This dog was a 5-year-old male castrated English Bulldog. This dog had no history of stones and no prior prevention diet had been attempted. No record of recurrence, urinalysis, and no comorbidities other than BOAS were documented for this patient. Innumerable (> 21) stones were visible on radiographs in this patient prior to removal. These stones were mineral opaque and ranged from < 1 mm to 3.6 mm in diameter.

Discussion

The radiopacity of uroliths helps to guide treatment decisions for veterinarians. Cystine and urate stones have previously been designated as radiolucent and their proper designation have informed both the selection for a proper prevention diet and the recommendation to investigate for comorbidities, particularly a portosystemic shunt.1,7,8 This is the first retrospective study to report the frequency at which cystine and urate stones are visible on survey digital radiographs prior to their removal. In our patient population, 27% of patients were diagnosed with either 100% cystine, urate, or stones of cystine and urate composition. The relative percentage of cystine stones in this study population is higher than prior published percentages and may represent a factor unique to a tertiary referral hospital or unique caseload of this institution. French Bulldogs are historically overrepresented with regards to cystine urolithiasis and are the second-most represented breed with cystine urolithiasis in this study population. Other studies are needed to confirm whether this change in relative percentage of cystine stones is due to rising popularity of the French Bulldog, a geographic-specific factor, or due to other reasons. Within this group, 89% of stones were visible on radiographs (86% urate, 92% cystine, 100% cystine/urate), whereas in 11% of cases they were not identified (14% urate, 8% cystine). This false-negative rate is much lower than previously published rates of false-negative for cystine and urate stones, with rates up to 20% to 25% cited in the literature.12,15

In our patient population, 13% of patients with cystine stones and 10% with urate stones had been trialed on a prevention diet prior to surgical or nonsurgical removal. All dogs started on a prevention diet for urate stones had a history of urate stones and 75% of the patients started on a prevention diet for cystine stones had a history of either cystine or urate stones. Of dogs that did not have a history of cystine or urate stones, 50% of these were started on an improper dissolution diet, one that dissolves struvite stones. This emphasizes the importance of starting a dissolution or prevention diet ideally after definitive determination of stone type, and also highlights a potential need for the development of an algorithm to increase suspicion of certain stone types prior to retrieval and analysis.

Similar to other published studies, we found an association between signalment and certain congenital abnormalities and stone type.1,2,8 A high proportion of the cases with cystine stones were intact males (87%) and brachycephalic (26%). Therefore, even the identification of a radiopaque stone when these factors are present may increase the suspicion of cystine stones. Additionally, the Dalmatian breed (26%), a history of urate stones (30%), or known presence or suspicion for a portosystemic shunt (37%), may increase the suspicion for urate stones even if a radiopaque stone is identified. We found that in 45% of cases, cystine crystals were identified on urinalysis in cases when cystine cystoliths were later identified. In one study, 63% of dogs noted to have cystinuria had cystoliths, but more studies are needed to determine the percentage of dogs with cystinuria that have cystoliths at the time of urinalysis.16 Ammonium biurate crystals were less common in our study, accounting for 21% in cases when urate cystoliths were identified. However, bilirubinuria and positive icotest was found in 50%. We found urine pH to be a less reliable marker for stone type for cystine stones, as the average pH in our study population for cystine stones (7.0) is higher than published.1,5 A larger sample size is needed to assess whether this study population truly has different urine pH, which may be related to cystine cystolith composition and their radiopacity, diet, or other factors. In our study population, the average urine pH of urate stones (6.5) matched published literature.1,5 These findings suggest that, in combination with other signalment factors and suspicion for comorbidities, that crystalluria should increase suspicion for cystine stones and bilirubinuria, and pH around 6.5 should increase suspicion for urate stones.

We found that there is great variability in the specific radiographic features of radiopaque cystine and urate cystoliths. The diameter of radiopaque cystine stones ranged from < 0.5 mm to 17.3 mm and the diameter of urate stones ranged from < 1 mm to 10 mm. While a recent study14 found that cystine and urate stones of > 1 mm in a phantom bladder are visible on digital radiography at high frequency, this study suggests that stones even smaller may be visible. Similarly, there were cases of both stone types in which the subject only had 1 visible stone, while in others innumerable stones were visible. Relative mineral opacity of cystine stones compared to urate stones could not be qualified because of differing radiographic techniques between subjects, patient variation in the degree of mineralization of bones, patient body condition, superimposition of calculi or other abdominal organs over the urinary bladder, presence of gas within the urinary bladder due to prior catheterization, and presence of wet hair artifacts. However, all visible stones were mineral opacity, which differs from the soft tissue opacity of the urinary bladder.

Limitations of this study are inherent to the retrospective nature. First, diagnostic protocols when stones were suspected could not be standardized, such that some cases may have bypassed radiographs in favor of another modality if cystine and urate stones were suspected prior to diagnosis. Additionally, while the majority of radiographs were taken at the University of Florida Small Animal Hospital, there
was a small percentage diagnosed via radiographs taken at their referring veterinarian. Therefore, differences may exist between x-ray machines, as well as the possibility that radiographic technique and exposure varied between institutions. This may have contributed to a higher false-negative rate of cystine and urate detection on radiographs in this study. Additionally, there is a possibility that urate and cystine stone composition varies at a microscopic level, such that different regions may have different frequencies at which stones are identified on radiographs. Lastly, a higher percentage of stones removed from this population were cystine and urate stones than is reported in the literature. This may be attributable to differences in clinical sequelae that cause dogs to be presented to a tertiary referral hospital, regional differences in stone composition, or recent popularity of breeds such as the French Bulldog.

These findings suggest that urate and cystine stones are commonly radiopaque and therefore when a stone is visible on radiographs, the radiolucency of the stones should not overshadow the consideration of signalment, presence of comorbidities, and urinalysis findings in the determination of certain treatment and diagnostic recommendations. These findings support that a thorough work-up of the patient including urinalysis and culture, diagnostic imaging, and biochemical analysis can be helpful in correctly identifying stone type prior to retrieval or prescription of a prevention or dissolution diet. Future studies should prospectively investigate risk factors for the formation of various stone types, such as breed, reproductive status, biochemical abnormalities, urinalysis, congenital, genetic, and acquired metabolic disease processes, to better guide diagnosis and treatment recommendations. Future investigation would also be benefitted by standardizing diagnostic practices across a patient population. Additionally, analyzing stone composition and density may identify regional differences in the likelihood of diagnosis using survey radiographs for historically radiolucent cystoliths.

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