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Kedide kalsiyum oksalat ürolitiazis olgusunda idrar mikrobiyom nakli: Taşlar neredeydi?

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Öz

Biz burada, tedaviye yanıt veren kalsiyum oksalat ürolitiazisi olan bir kedide üriner mikrobiyom transplantasyonunu (uMt) tarif eden yeni ve çığır açıcı bir müdahale olarak tanımladık. Bu durum belgesinde, yani bir vaka raporunda, kalsiyum oksalat ürolitiazisi olan bir kedinin idrar mikrobiyomunda görülen farklılıkların hastalık durumuyla ilişkili olabileceğini varsaydık. Bu nedenle, üriner sistemin mikrobiyocoğrafyasını tam uMt (sağlıklı, yaş/cinsiyet uyumlu bir donörden doğrudan kateterli ve hastalıklı alıcı kediye verilen) yoluyla değiştirmeye karar verdik. 72 saatlik süreçte klinik bulgular kaybolan hastanın, takip eden 8 haftalık takip döneminde hematüri ve strangüri görülmedi. İdrar tahlili ve kan kimyası sağlık durumuna çevrildi ve radyografinin yeniden değerlendirilmesinde tespit edildiği üzere kalsiyum oksalat taşları yerinden kayboldu. Yazarların mevcut bilgisine göre bu, ürolitiazisli bir kedide tedaviye yanıt veren tam uMt'ye ilişkin ilk rapor olacaktır. Tedavi protokolleri, yanıt vermeyen eski moda ilaç tedavisinin yerini alabilecektir. Üstelik bu teknik, en azından seçilmiş vakalarda gereksiz cerrahi müdahalelerin yerine geçebilecektir. Bu eşsiz çığır açıcı doğal müdahale, önümüzdeki gelecekte birçok kedide ürolitiazis vakasına yardımcı olabilecektir.

Anahtar Kelimeler: idrar yolu, kedi, mikrobiyom, transplantasyon, ürolitiyazis.

Urinary microbiome transplantation in a feline calcium oxalate urolithiasis case: Where were the stones?

Abstract

We herein as a novel and breakthrough intervention described urinary microbiome transplantation (uMt) in a cat with calcium oxalate urolithiasis that respond to treatment. In this position paper, namely a case report, we hypothesized that differences in the urinary microbiome of a cat with calcium oxalate urolithiasis, would be associated with disease status. Therefore, we decided to change the microbiogeography of the urinary system through complete uMt [from a healthy, age/sex matched donor to recipient directly given to catheterized and diseased cat]. Clinical signs disappeared in the 72 hours period, in which hematuria, stranguria were no more evident for the following 8 weeks follow up period. Urinalysis and blood chemistry were switched to health status and calcium oxalate stones were dislodged as detected by re-evaluation of radiography. To the present authors knowledge this would be the first report for complete uMt in a cat with urolithiasis gave respond to treatment. Treatment protocols would replace old-fashioned drug therapy without response. Moreover, this technique would substitute unnecessary surgical interventions at least in selected cases. This unmatched breakthrough natural intervention should have helped several feline urolithiasis cases within the next future.

Keywords: Cat, microbiome, transplantation, urinary, urolithiasis.

Introduction

Given microbiota have been considered bunches of ecological groups comprising commensal/symbiotic/pathogenic microorganisms; microbiome could participate in renal stone exhibition via i) hyperoxaluria and calcium oxalate supersaturation, ii) biofilm generation and accumulation and urothelial bruising. Responsible bacteria attach to calcium oxalate crystals, subsequently give rise to pyelonephritis and cause alterations among nephrons. Urinary tract microbiome, dissimilar with the gut microbiome, could be discriminated between subjects with or without urinary stone disease (Jung et al., 2023). Considering people with the urine microbiota, participating urease-producing bacteria (*Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Providencia stuartii*, *Serratia marcescens*, and *Morganella morganii*) are responsible within stone formation. *Escherichia coli* and *K. pneumoniae*, are two uropathogenic bacteria, in which their abundance could be related to calcium oxalate crystals existence. Furthermore, *S. aureus* and *Streptococcus pneumoniae* are examples of non-uropathogenic bacteria with calcium oxalate lithogenic effects (Wang et al., 2021). On the other hand, Lactobacilli and Enterobacteriaceae taxa are commonly detected in healthy subjects and splitted from urinary stone diseased ones (Zheng et al., 2020).

Given feline urinary tract diseases result with significant morbidity and mortality and subclinical bacteriuria might be detected, few data existed on urinary microbiome in cats. In a prior case-control research feline urinary bladder microbiome were analyzed in cats with chronic kidney disease, idiopathic cystitis and positive urine culture samples. Out of 108 urine samples from cats 19 phyla, 145 families, and 218 genera were determined. Highest ranking abundances were Proteobacteria and Firmicutes. Dominant urotypes by Escherichia-Shigella were exhibited in 53% of chronic kidney disease (Kim et al., 2021).

In the present case report the aim was to detect i) gut microbiota analytes through Midog® Pet Microbiome Testing via next generation sequencing, ii) switch urinary microbiome from disease status to probable healthy urinary system via breakthrough uMt in a cat with calcium oxalate urolithiasis.

Case presentation

The present case was a Scottish Fold short hair cat at the age of 6 years with 3.5 years history of chronic enteropathy not giving respond to drug prescription. We at our Feline Dermatology Group (FDG) practice, available at Intestinal Permeability Measurement Center (IPOM) received natural polyphenol treatment (Gut-cumin I® Liquid Solution, Larek Tarım, Ankara) and relevant probiotics for 3 months of era and complete resolution of gastrointestinal signs were evident giving respond to this natural treatment intervention. However later on the cat was brought to our FDG practice at IPOM facilities, with hematuria and stranguria. Laboratory analysis [complete urinalysis, serum biochemistry, hematology, gut microbiota analytes, gastrointestinal biomarkers and abdominal radiography] revealed calcium oxalate urolithiasis. We then immediately decided to change urine microbiogeography by professionally planned uMt. Prior to uMt gut microbiota analytes were deemed available shown at Table 1 below.

Procedures and interventional treatment

Briefly another 3 years old otherwise healthy cat, from another household, was referred to the clinic at the same time with the diseased cat. Both owners were sisters, however cats were not siblings. Both cats had different feeding and management conditions, and donor was routinely vaccinated, also received anti-parasitic treatment scheduled by another veterinary surgeon. At the time of referral, the donor was checked for physical examination and catheterized gently, urine was withdrawn and a small portion of it was suddenly checked for complete urine analysis and urinary dipsticks. There was no health issues detected on analytes. Figure 1-3 showed algorithmic interpretation in the present case with all results available, showing treatment efficacy with uMt.

Table 1. Listed were to those of bacteria determined/identified in the fecal specimen with probable clinically relevance. Microbial compositions were shown at species level, as detected by Midog® Pet Microbiome Testing via next generation sequencing. Entire species levels were rounded to 100% (data not necessary to shown)

Species detected	Percentage
Bacteriodes fragilis	5.98%
Escherichia coli	6.2%
Escherichia coli-fergusonii	0.5%
Terrisprobacter glycolicus	2.21%
Terrisprobacter mayombei	0.43%
Enterobacter cloaceae	1.28%
Klebsiella aerogenes-granulomatis-pneumoniae	0.1%
Klebsiella aerogenes-pneumoniae	0.48%
Klebsiella pneumoniae	0.2%

Discussion and Conclusion

Given urine obtained from apparently healthy dogs is not sterile, a prior study was aimed to detect biodiversity of microbiome in urine of 50 clinically healthy dogs via cystocentesis. In that study conventional culture did not yield positive results in

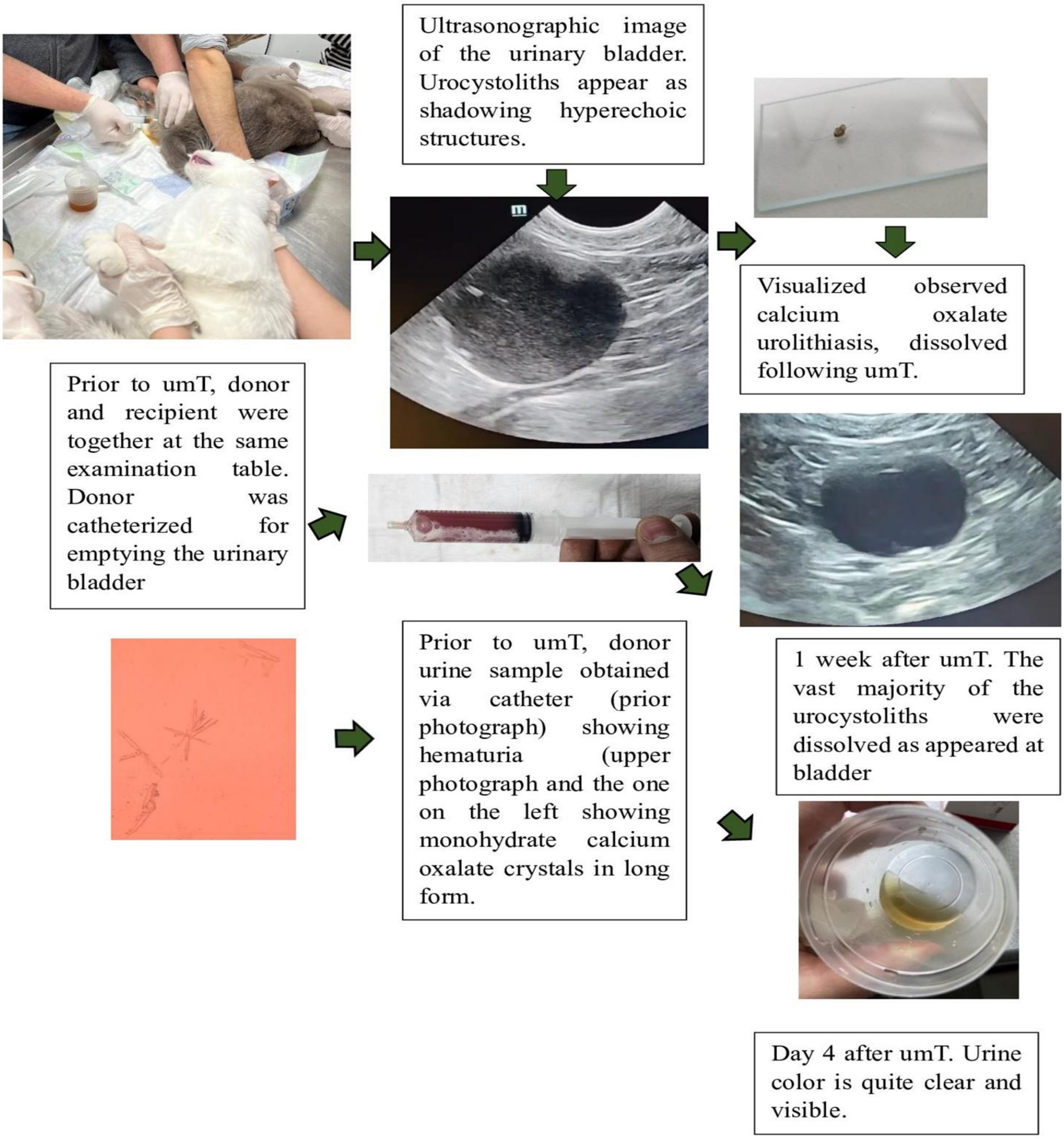

Figure 1. Algorithmic interpretation for the present case indicating both diagnosis and treatment modality for uMt.

Figure 2. uMt showing urine sample transportation, as previously and just prior to, recipient.

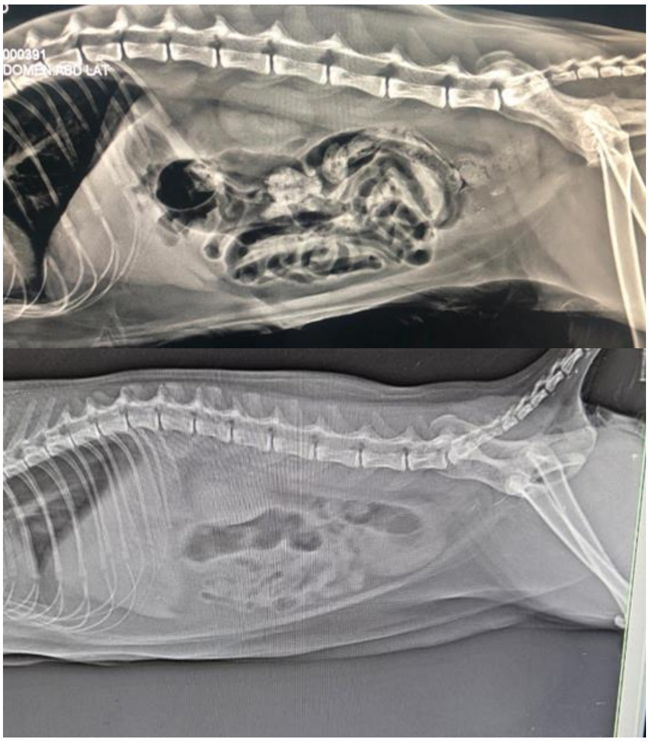

Figure 3. Lateral abdominal radiograph of present case castrated male domestic shorthair cat presenting one large and several other relevant small, scaled calcium oxalate dihydrate urocystoliths (red area). On the other hand, the photograph taken at the 5th day of umT, showed disappearance of urocystoliths.

any samples, whereas next-generation sequencing exhibited low presence of bacteria/fungi in entire samples with varying diversity and abundance. Struvite crystals were in relation with microbiota structure along with a positive correlation on pH (Melgarejo et al., 2021). On the other hand, participation of gut microbiome linked to those pathological mechanisms remained unclear until a near past era (Ticinesi et al., 2019). Available data identified that depleted *Oxalobacter formigenes* (Ticinesi et al., 2019), oxalate-degrading capable Gram-negative anaerobic species was linked to calcium oxalate nephrolithiasis (Ribeiro da Silva et al., 2009). In the present case gut microbiota analytes did not reveal relative abundance of *O. formigenes*, which could contribute to formation of calcium oxalate urolithiasis exhibited by this case

Urine, without accompanying urinary tract infection, has long been suggested to be sterile; an opinion still considered in several veterinary healthcare professionals to date. However, we need to address a very famous discourse of Thomas Shelby based on a Netflix Movie 'Peaky Blinders', the past is no more concern. Furthermore, evidence conflicting to this idea has been assembling for long duration (Thomas-White et al., 2016). Culture-positive bacteriuria without any symptomatology is frequently detected within women and older aged people; indeed, the latter condition has been denominated as "contamination" based on bacterial analysis < 105 (Kass, 1962). In the present case although culture was not available, we could not speculate that urine was sterile in this case.

To the present authors' knowledge, this may be the first report indicating total intervention of uMt and its success. First author (K.U.) thought, hypothesized, organized, planned and be a frontier for this technique, probably that has not been mentioned or published. Total replacement of urinary bladder content (after emptying and fulfilling with donor urine) with urine microbiota transplantation could thus either be a breakthrough solution for calcium oxalate urolithiasis. Although solely 1 case was involved in this paper, further warranted larger scale and population of cats with calcium oxalate urolithiasis must be involved in an attempt to better investigate and probably establish the efficacy of this technique. Our subsequent study and projects would thus be aimed at this route. However, we were keen on publishing this paper, as because several cats are suffering from this condition, entirely subjected to surgical intervention. However, if there is no complete urinary obstruction, this intervention should substitute unnecessary operational decisions.

Just prior to 40 years pat background, calcium oxalate exsitance was suggested to be rare among cats. Afterwards, calcium oxalate urolithiasis incidence was elevated from 2% (1984) to nearly 50% (1999) (Elliott and Vernon, 2003). This was followed by a sharp elevation over the last decades, accompanied by a subsequent corresponding decline within the presence of struvite uroliths (Dijcker et al., 2011). The latter elevation could be briefly explained, probably, with magnesium narrowed acidifying diets (Elliott and Vernon, 2003). Nearly 90% of urocystoliths are frequently detected within the bladder, other relevant ones in the kidney/ureters (Elliott and Vernon, 2003; Dijcker et al., 2011). In the present case there was no complete obstruction, and urocystoliths were detected on urinary bladder and urethra.

In a prior and well-established study regarding highlighted feline urinary tract diseases and the urinary microbiome; to those of cats with chronic kidney disease (CKD), feline idiopathic cystitis (FIC), and positive urine cultures (PUCs). In a total of 108 urine samples obtained from diseased cats, detected that the feline bladder microbiome is sparsely characterized. Proteobacteria and Firmicutes, were respectively abundant along with four major urotypes]i.e. Escherichia-Shigella or Enterococcus and other relevant ones]. Briefly, the overall microbial diversity for cats with CKD, presented more similarity to that of E. coli PUC cases in contrast to control cats (P <0.001), whereas PUC cases microbial diversity was different from controls, CKD or FIC cases (Kim et al., 2021). On the other hand, Balboni et al. (2024) in a very recent article, feline idiopathic cystitis was denoted with non-appearance of existing bacteria nor bacterial DNA within the urinary bladder. Moreover, another interesting article, with special concern of us, published on 29.05. 2024 investigating the intestinal and urinary microbiota of 9 cats with kidney stones were comparable to 9 other healthy cats prior to, during, and following treatment with the antibiotic. At the starting point cats exhibited kidney stones presented a less diverse gut microbiota. Moreover, antibiotic prescription diminished microbiota diversity. Lack of specifical gut microbiota might prone absent functioning of latter bacteria, i.e. oxalate degradation, probably could trigger calcium oxalate stone formation. Available data prompted an association among diminished gut microbiota richness and diversity and the risk of kidney stone formation in cats. Among cats with lithiasis could probably presented absence of oxalotrophic bacteria caused weakened degradation of oxalate within the intestinal location, increased intestinal absorption of oxalate, and finally hyperoxaluria (Joubran et al., 2024).

In the present case as aforementioned relative abundance of *E. coli, E. coli-fergusonii, K. aerogenes-granulomatis-pneumoniae, K. aerogenes-pneumoniae and K. pneumoniae*, were 6.2, 0.5, 0.1, 0.48 and 0.2%, respectively which could contribute disease pathogenesis at the present case. In conclusion it should not be unwise to draw preliminary conclusion that uMt should have helped stones were dislodged, which could change and substitute feline calcium oxalate urolithiasis in near future.

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