When Milo Opened Pandora's Box

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Class of 2021

Clinicopathologic Conference

July 13, 2020

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Introduction

FLUTD, FUS, FIC, Pandora Syndrome; all confusing and interchanging terms for one of the most common urinary diseases in felines. Feline Lower Urinary Tract Disease (FLUTD) refers to any disorder that affects the urethra and/or the urinary bladder that could be caused by various etiologies including infectious agents, urethral plugs, uroliths, tumors, anatomical abnormalities, or trauma[24]. However, sometimes, no specific cause can be found for the associated signs of lower urinary tract disease (LUTD) that includes stranguria, dysuria, hematuria, pollakuria, and/or inappropriate urination. In these cases, Feline Idiopathic Cystitis (FIC) is utilized as a diagnosis and is known to be the most common cause of FLUTD in cats, accounting for up to 55-65% of cases[18].

FIC is defined as an acute or chronic disease of waxing and waning signs of irritative voiding, sterile urine, absence of cellular abnormalities suggesting neoplasia, and failure to identify an alternative cause for these signs after appropriate lower urinary tract imaging procedures[7]. To make things even more confusing, Feline Interstitial Cystitis (FIC) refers to a subset of cats with idiopathic cystitis that appear to have an increase of their stress response system and decreased adrenocortical function to common stressors[2]. Pandora Syndrome is a newer term that encompasses criteria that commonly are associated with chronic lower urinary tract signs such as persistence or recurrence of the condition over months to years, additional comorbidities, historical early adverse experiences, and/or evidence of familial involvement[7].

This confusing terminology has fluctuated with our better understanding of lower urinary diseases of felines, as much of the research now points toward the hypothesis that systemic psychoneuroendocrine factors, exacerbated by chronic stressors, plays a large role in this disease[14]. Several studies have revealed specific risk factors for FIC that comprise of

environmental and husbandry factors, especially indoor lifestyle, type of litter, dry diet, cohabitation/conflict with additional cats, lack of environmental enrichment, obesity, and age[3,18,26]. Therefore, FIC cats tend to "fit a profile" that includes young to middle aged, overweight, mainly indoor sedentary lifestyle who lives with other cats and potential stressors and are of a nervous disposition[22].

History and Presentation

Milo is an 8-year-old male neutered domestic shorthair feline who presented to MSU-CVM Small Animal Internal Medicine Department on March 2, 2020 for a urinary obstruction of presumptive functional etiology. Functional etiology refers to a urethral obstruction resulting from a urethral spasm owing to the inflammation associated with FIC[25]. Milo's owners and referring veterinarian reported that he has had recurring urinary tract issues since he was very young. At all episodes, no definitive diagnosis could be made for the urinary signs Milo was experiencing such as stranguria and hematuria. Additionally, over the past three years, three different urine cultures have been performed at various flare-ups and all have resulted in no growth at 24-48 hours. His owners had noted Milo to be an easily stressed individual, therefore he had been maintained on transdermal fluoxetine and prazosin during times of high stress or suspect flare-ups of his urinary condition. He lives with four other cats who all have supervised access outdoors but are mainly indoor pets. Milo was currently being maintained on a Hill's Science Diet formulation that was labeled to have gastrointestinal, urinary and weight reduction benefits.

On February 29, 2020, Milo was noticed to be actively straining with minimal production of bloody urine by his owners. The next day, he was administered a double dose of fluoxetine, however his condition did not improve and on Monday, March 2nd he was noted to be laterally

recumbent and minimally responsive. Milo was admitted to his primary veterinarian, where a large softball sized bladder was noted on ultrasound. A cystocentesis was then performed and placement of a tomcat catheter to allow urine flow. A urinalysis revealed severe hematuria with a specific gravity of 1.050. The most concerning findings on bloodwork revealed a severe increase of BUN at >180 mg/dl (10-30), severe increase in creatinine at 17.8 mg/dl (0.3-2.1), and severe hyperkalemia at >8.5 mmol/L (3.7-5.8). As studies have shown, the longer the obstruction period has elapsed, the higher the levels of uremic metabolites, urea, creatinine and electrolytes will be and a clinical screening examination that includes monitoring of blood pressure, electrocardiogram, biochemical and blood gas analysis is justified for obstructive cases[17,26]. Additionally, hyperkalemia in obstructed cats has been suggested as a risk factor for mortality[26]. No grit or stones were palpated at this time, suggesting a potential functional urethral obstruction versus a mechanical one, however radiographs were not performed to confirm this. On ECG, several runs of premature ventricular complexes were seen. Milo was administered LRS intravenously (45 ml/hr bolus) via an intravenous catheter before referral to MSU-CVM Small Animal Internal Medicine Service for further work-up and discussion for surgical intervention.

On presentation, Milo was bright, alert, and responsive. Both the tomcat catheter and the intravenous catheter were still in place and patent. His vital parameters were within normal limits, however his rectal temperature was low at 98.1° F. His mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. Cardiothoracic auscultation was within normal limits and a normal sinus rhythm was appreciated on ECG. His femoral pulses were fair and synchronous with his heartbeat. His SpO2 was 95% and he was hypotensive with a mean arterial pressure of 59 mmHg. On AFAST, his bladder appeared small with a thickened wall. At

this time, a fluid bolus of LRS was administered intravenously to help improve the hypotension and previous hyperkalemia and azotemia.

An iStat was performed which revealed a metabolic acidosis and marked hypocalcemia. More blood was collected after the fluid bolus for a CBC and chemistry panel. The CBC revealed a stress leukogram and the chemistry revealed a mild hyperkalemia at 5.8 mmol/L (3.50-5.50), mild hyperglycemia at 163 mg/dl (70-160), marked increase in BUN at 179 mg/dl (10-40), moderate to marked increase in creatinine at 11.54 mg/dl (0.40-2.00), moderate hyperphosphatemia at 11.5 mg/dl (2.6-5.7), mild to moderate hypocalcemia at 6.8 mg/dl (8.2-10.6), and a moderately high CK at 757 U/L (50-225). At this point, Milo was started on a constant rate infusion of lactated ringer's solution (6.5 ml/kg/hr, 2.5x maintenance rate), buprenorphine (0.015 mg/kg), and prazosin (0.06 mg/kg). Urine quantification, bladder ultrasounds and urinary catheter care was also implemented into Milo's continued care while further diagnostics were discussed.

Diagnostic Approach/Consideration

The diagnosis of FIC is solely a diagnosis of exclusion and relies heavily on signalment, history of the cat and environmental factors, exclusion of other lower urinary causes and response to therapy[27]. Therefore, results from common diagnostic measures are often normal from cats with FIC, but in some instances may reveal focal or diffuse thickening of the bladder wall[12]. With Milo's long-term history of urinary problems with no definitive diagnosis, stressful nature, and bladder abnormalities seen on initial ultrasound, we could initially diagnose him with FLUTD and continue with our diagnostic exclusion plan. In the meantime, Milo was stabilized and admitted to the hospital for continued monitoring that included collecting blood for serial testing to monitor his azotemia and hyperkalemia as well as urine quantification to ensure that he

was adequately producing urine and prevent other potential obstructions. A fentanyl CRI (2 mcg/kg/hr) and gabapentin (13 mg/kg) was added to his treatment regimen at this point to help manage his pain and anxiety.

On March 4, Milo was sedated with dexmedetomidine (5 mcg/kg) for abdominal radiographs and an abdominal ultrasound. On radiographs, the bladder was moderately to severely distended. The left kidney revealed evidence of a mineral opaque structure over the caudal pole. On ultrasound, the renal pelves and proximal ureters were mildly to moderately dilated bilaterally. The ventral aspect of the urinary bladder wall was thickened, and there was a large, irregularly shaped, smoothly marginated, hyperechoic structure that projected into the lumen that was suspected to be a potential polyp. There was a moderate amount of hyperechoic debris within suspension in the urinary bladder. At this point, uroliths, major anatomic abnormalities, and obvious neoplasias could be ruled out.

Due to the length of time Milo had been suffering from this disease with minimal relief from medical management, the high number of historical obstructive related episodes, and the inconclusive findings via diagnostic measures of other definitive urinary issues, Milo was diagnosed with FIC and plans were made to prepare for a perineal urethrostomy and cystotomy. Over the course of the next two days, Milo's azotemia and hyperkalemia were corrected and instead developed metabolic alkalosis and hypokalemia which were then corrected with appropriate fluid therapy that included 0.9% sodium chloride and potassium chloride. His prazosin was discontinued.

Pathophysiology

Feline Idiopathic Cystitis (FIC) can be divided into unobstructed and obstructed scenarios. As stated earlier, functional urethral obstructions can occur, but mechanical

obstructions happen frequently and are caused commonly by urethral plugs. Urethra plugs consist of a matrix of mucoprotein and inflammatory debris and predominately struvite crystals[9,11]. There has been some evidence that urethral plugs may contain Tamm-Horsfall mucoprotein, which may be a local host defense against bacterial and viral urinary tract infections[9].

The typical clinical course of FIC is illustrated by episodes of LUTS that resolve spontaneously within 3-5 days regardless of treatment; however, there is a small subset of cats that chronically exhibit these signs for weeks to months or are prone to have frequent reoccurrences[9]. This chronic form of FIC, or sometimes called feline interstitial cystitis, shares many features in common with human interstitial cystitis and research findings in human IC have resulted in similar correlated hypotheses of pathophysiology in FIC[1,9]. There can be multiple abnormalities at play to lead to the clinical manifestations of FIC including, intrinsic, urothelium, submucosa, afferent/efferent inputs, neuronal, hormonal, immunological, as well as comorbid disorders and potential adverse early life events[5].

Glycosaminoglycans (GAGs) are a component of the glycocalyx that covers the transitional epithelium of the lower urinary tract (LUT) and works to prevent bacterial and crystal adherence as well epithelium protection from toxic substances[14,21]. Decreased total excreted GAG, especially GP-51, has been reported in FIC cats which has shown to lead to chronic exposure of bladder wall tissues to urine constituents, which in turn results in sensory nerve stimulation, mast cell activation, and/or induction of immune-mediated or neurogenic inflammation[14]. In one study, urinary GAG excretion was three times greater in 24-hour urine samples from normal cats versus FIC cats[1]. Additionally, cats with FIC have been shown to have significantly higher functional and anatomical abnormalities of the urothelium, which is a

specialized epithelium of the LUT that works to maintain tight junctions to prevent large influxes of ions and solutes[5]. Transmission electron microscopy studies in FIC cats have shown a thin, erosive, and ulcerated urothelium leading to the hypothesis that not only is permeability altered as with decreased GAGs, but the cells and their receptors/transmitters that make up this layer have been altered leading to abnormalities in urothelial differentiation, repair, and signaling[5,9,14].

In addition to structural or functional defects in the urothelial barrier, injury-induced alterations in urothelial release chemical signaling molecules (like nitric oxide or acetylcholine) may also activate sensory afferent neurons and mast cells[1]. It has also been shown that FIC cats have an increased sensory nerve fiber density, and therefore their sensory nerve fibers are more sensitive to stimuli[1,5]. These fibers, otherwise known as pain fibers, C-fibers, or substance P receptors, can be triggered via the previously discussed pathways (defective GAGs or urothelium) or in response to central triggers, such as stress through the sympathetic nervous system[10,25]. This stimulation of C-fibers that results in the well-known hypothesis coined "neurogenic inflammation" correlates with the histopathology findings of bladder biopsies from FIC cats that often reveal submucosal edema, hemorrhage, fibrosis, changes in cell density, urothelial erosion, vasodilatation, and vascular leakage[1,5,9,25].

The submucosa of FIC cats has also shown an increased number of mast cells which are highly activated by damaged or dysfunctional urothelium[1]. Furthermore, human interstitial cystitis studies have shown that urinary mast cells and neuropeptide-containing neurons have a close biochemical and anatomical relationship, strengthening the suspicion that mast cells play a central role in the pathogenesis of FIC[14].

Another factor at play is the increased sympathetic drive of FIC cats that is directed by increased tyrosine hydroxylase immunoreactivity and plasma norepinephrine concentrations, and

decreased sensitivity of alpha-2-adrenoceptors[14].Tyrosine hydroxylase is the rate-limiting enzyme of catecholamine synthesis which is found in the parts of the brain such as the pontine locus coeruleus and the paraventricular nucleus of the hypothalamus[5,12]. The locus coeruleus contains the largest number of noradrenergic neurons and is the most important source of norepinephrine in the CNS. It is involved in both external and internal input responses, such as bladder distention or external stimuli that are termed “stressors” in this case, such as psychosocial stress which is one of the most common and influential stressors of many species[25]. Due to the fluctuation of inputs being received by the locus coeruleus, hypotheses have been made suggesting that this may point to the “waxing and waning” course of FIC[5]. The decreased sensitivity of alpha-2-adrenoceptors was identified via *in vivo* and *in vitro* studies using medetomidine that resulted in FIC cats demonstrating a decreased effect from the drug versus normal, healthy cats[5].

In patients suffering from extreme chronic stress, the normal HPA system that involves cortisol inhibiting the sympathetic nervous system outflow to act as a negative feedback on the hypothalamus and adrenal glands to inhibit its own release is disrupted leading to an overall heightened response to stressors[25]. In one study, FIC cats had a significantly decreased cortisol response to administration of synthetic adrenocorticotropic hormone and many often had smaller adrenal glands than normal cats[9]. In other words, there is evidence to suggest that FIC results in an overactivation of the sympathetic nervous system with a suboptimal activation of the HPA axis[12].

Studies have shown that FIC cats are likely additionally suffering from a comorbidity, including behavioral, cardiovascular, endocrine, or gastrointestinal issues[5]. For example, general lower urinary tract signs in cats have been reported to be co-morbid with separation anxiety

syndrome, hypertrophic cardiomyopathy, and obesity[4]. Lastly, it is important to remember that what an individual cat finds "stressful" also depends on a variety of factors that also may play a role in the pathogenesis, including genetics, socialization experiences, specific learning, and coping strategies[25].

Treatment and Management

There is no cure for FIC but over the many years of copiously studying this disease, numerous agents and procedures have been formulated and recommended for treatment and prevention of FIC. Despite these various therapies, there has been abundant debate regarding efficacy and, in most cases, insufficient research to support these therapies. As of today, the current standard of care for cats with FIC includes environmental enrichment, stress reduction, feeding moist food (>60% moisture), increasing water intake, various pharmaceutical agents (analgesics, anti-inflammatories or anxiolytics), as well as effective client communication[6,8].

Studies conducted on felines in research settings have revealed that when subjected to an environment lacking from stimulation or predictability, cats have shown to have decreased activity levels and increased hiding behaviors[2]. Multi-modal environmental modification (MEMO) is defined as an institution of changes in the cat's environment to attempt to reduce LUTS by decreasing the likelihood of activation of the stress response system[2]. This protocol attempts to include and extend the concept of environmental enrichment to include as many features of the cat's environment as possible[2]. Goals such as providing all necessary resources (i.e. proper feeding stations, appropriate litterbox management, resting places, scratching posts, etc.), enhancing interactions with owners, minimizing conflict, and making any changes gradually are typically recommended[8]. This is one recommendation for treatment/prevention of FIC that has shown significant clinical and statistical reduction in LUTS in felines[2].

Nutritional management together with methods to increase water intake have been recommended to dilute the urine to decrease the concentration of substances that may be contributing to the underlying pathology[8]. Regardless of this theory, there have been limited research on diets in FIC cats, however some studies have shown benefits from moist therapeutic diets versus dry food by reducing clinical signs[16]. Specific nutrient profiles have not been established for FIC, however one limited study had shown that a low-magnesium, urinary-acidifying, omega-3 fatty acid- and antioxidant-enriched prevention diet helped to reduce the rate of recurring clinical signs[13]. There are multiple other means to increase water consumption besides a canned diet, however there is no research to support these measures.

In some individuals, pharmacological therapy is warranted. FIC cats commonly have increased concentrations of urinary and serum pro-inflammatory proteins, such as fibronectin, thioredoxin, IL-12, and IL-18. Additionally, a discovery was made that revealed FIC bladders express increased cyclooxygenase, which has emphasized the use of non-steroidal anti-inflammatories, but studies have not shown a clear benefit and side effects of NSAIDs should be considered[18]. This disease is hypothesized to be extremely painful, as extrapolated from human interstitial cystitis cases, which has led to the use of analgesics. Male cats may benefit from antispasmodic drugs to relax the urethra, such as prazosin or phenoxybenzamine[11]. Anxiolytics, such as amitriptyline, gabapentin, fluoxetine, or clomipramine, are sometimes utilized in more chronic cases. Specifically, amitriptyline and clomipramine in studies have indicated successful in decreasing LUTS[6]. Other agents such as glycosaminoglycan replacement drugs or pheromone sprays have shown promising therapeutic relief in many instances.

In some cases, recurrent obstruction continues to occur despite ample medical, nutritional, and environmental management. To provide a better quality of life for these cats,

surgical intervention is justified. A urethrostomy is the surgery of choice and in cats the most common approach being perineal. A perineal urethrostomy (PU) involves creating a permanent stoma in the wider pelvic urethra via anastomosis to the perineal skin and amputation of the narrow penile urethra[19]. This surgery has been described to provide a good long-term quality of life in conjunction with medical management according to owners in several studies[19]. However, there have been several complications reported including urethral strictures, recurrent bacterial urinary tract infection, urolithiasis, and rarely, wound dehiscence, extravasation of urine, urinary or fecal incontinence, hemorrhage, rectal prolapse, perineal hernia and rectourethral fistula[19].

Many studies have pointed to recurrent UTI's as being the most common and important complication[19,23]. Several factors may play into the increased occurrence of UTI's following a perineal urethrostomy such as the decreased length of the urethra, loss of penile urethral mucosal defense mechanisms, increased diameter of external urethral orifice, impaired striated urethralis muscle function and decreased intraluminal pressure, comorbidities in the remaining portion of the urinary tract that is predisposed, and/or the use of a transurethral catheter post-op[20]. Urethral strictures most often occur at the mucocutaneous junction and are often associated with self-trauma or poor surgical handling[19,20].

Post-operative recommendations include IV fluid therapy to continue to correct systemic derangements that may have been present pre-operatively, urination output monitoring, analgesics for 3-5 days, E-collar maintenance, monitoring for UTI signs with concurrent urinalysis and appropriate antibiotic therapy if infected[19,20]. One of the most important aspects to keep in mind is that this procedure is not a "definitive" treatment for FIC, as there is no cure. Therefore, even though a PU has been shown to reduce the rate of obstruction, the pathology associated with FIC is not resolved, and lower urinary tract signs can still occur. Consequently,

no matter if medical or surgical intervention is chosen, a critical piece to management of FIC cats is client communication.

Case Outcome

On March 6, Milo underwent a perineal urethrostomy and cystotomy with no complications. He was continued on his fentanyl CRI (3 mcg/kg/hr) and his LRS CRI was now being maintained at maintenance (2 ml/kg/hr). Upon opening the bladder, the walls were severely thickened and erythematous with a presumptive polyp at the level of the right ureter internally. A biopsy was taken of the bladder wall for interpretation and culture/sensitivity. The urethra was intact with no tears.

After surgery, Milo recovered well and started to urinate normally about 2-3 hours post-operatively. He was administered his first dose of a 3-day course of Robenacoxib orally (2 mg/kg) later that evening. His stoma site and cystotomy incision continued to stay clean, dry, and adequately apposed. His fentanyl CRI was discontinued on the morning of March 7, and Milo was switched to buccal Buprenorphine (0.01 mg/kg). As Milo continued to do well post-operatively and his stoma site/cystotomy incision were clean and intact, his fluids were discontinued the morning of March 7th, and he was discharged later that day. Milo was sent home with buccal Buprenorphine (0.01 mg/kg) for 7 days and oral Robenacoxib (2 mg/kg) for 2 days. The bladder wall biopsy revealed inflamed tissue with mixed inflammatory infiltrates, hemorrhage and ulceration with a mass composed of a fibrin clot; however, no polyp or neoplastic evidence was appreciated. The culture and sensitivity of the bladder wall grew *Enterococcus faecalis* from enrichment broth, and consequently, oral Clavamox (13.75 mg/kg) was prescribed. Milo continues to do well at home and has had no urinary related issues since surgery.

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