

Mattis's Booty Scootin' Good Time

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Class of 2021

Clinicopathological Conference

November 20, 2020

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**Introduction:**

Perianal fistulas, also known as anal furunculosis, is an immune-mediated disease described in canines with German shepherd dogs being the most affected. Perianal fistulas are ulcerative or erosive lesions of the perineal area that do not commonly communicate with the rectum and anal sacs. Because the perianal fistulas do not communicate with the rectum, a sinus tract is the more appropriate term for the lesion. Surgical intervention has previously been thought as the recommended treatment, but current literature suggests that medical management is the standard of care. Multimodal therapy is preferred due to the synergistic effects of drugs leading to decreased dosing. The pathophysiology of perianal fistulas is not fully understood, but several processes are thought to contribute to the development of disease.

**History and presentation:**

Mattis is a 1 year and 10-month-old male neutered German Shepherd dog. Mattis was presented to Mississippi State University College of Veterinary Medicine's Dermatology Service on October 31, 2019, for an initial complaint of bilateral anal gland rupture with concurrent pruritic pinnae. Mattis initially presented to his referring veterinarian in July 2019 for unilateral anal gland rupture. Mattis had received enrofloxacin, amoxicillin/clavulanic acid, orbifloxacin, carprofen, and Hypochlorous Acid (0.010%) without response. Mattis also has a history of cryptorchidism characterized by a left abdominal testicle. He was up to date on all recommended vaccinations and parasitic preventatives.

On presentation, Mattis was anxious but alert and responsive. He weighed 33 kg and was a body condition score of 5 out of 9. His mucus membranes were pink and he had a capillary refill time of less than 2 seconds. On cardiopulmonary auscultation, Mattis had a pronounced sinus arrhythmia with synchronous heartbeats and femoral pulses. He had a heart rate of 48 beats

per minute, and he was panting so an accurate respiratory rate was unobtainable. A rectal temperature was not attempted due to his presenting complaint and sensitivity to the perianal region. Mattis's pinnae were erythematous with waxy ceruminous brown debris present bilaterally. Mattis had bilateral deep (measurements not taken) perianal lesions approximately 3cm in width located ventrolateral to the anus. Multifocal areas of ulceration were present between the two large fistulating lesions. The perianal region was wet and a mucous secretion was present. The palmar and plantar aspects of Mattis's four paws were mildly erythematous. His nails were overgrown. The remainder of this exam was within normal limits.

### **Diagnostic approach**

On presentation, a full physical exam was not performed due to discomfort of the affected area and an anxious patient. Further evaluation of the painful perianal lesions was necessitated; therefore, a complete blood count and serum chemistry were obtained before sedating Mattis with dexmedetomidine. Once sedated, an aural cytology was performed. Additionally, the perianal lesions were assessed via rectal examination and exploration using cotton tip applicators to determine if there was communication with the rectum. The area around the lesions was clipped and the fistulas were flushed and cleaned with dilute chlorhexidine solution. After superficial cleaning, a sterile culturette was used to obtain a sample from the deepest portion of the lesion and submitted for aerobic culture. The lesions were then measured and photographs were taken to track progression throughout the course of treatment.

Mattis's complete blood count revealed a slight lymphopenia of 10% (12-30) and a slightly decreased lymphocyte count of 1107 (1200-6500). Serum chemistry revealed a mildly decreased CO<sub>2</sub> of 17.9 (20-28).

The ear cytology was stained with Diff-Quik stain and immediately evaluated. The swab of the right external ear canal revealed 0 to 4 yeast in every other high-powered field with no cocci visualized. The left external ear canal produced 3 to 5 yeast per high powered field with too numerous to count cocci in most fields. The aerobic culture of the perianal fistula produced no bacterial growth at both 24 and 48 hours.

### **Pathophysiology**

Perianal fistulation is an immune mediated disease in which the pathophysiology is not completely elucidated. A breed predilection for the German Shepherd dog, Beagle, Border Collie, Australian Shepherd, Irish Setter, Chesapeake Bay Retriever, Leonberger, Staffordshire Bull terrier is seen, with the German Shepherd dog being the most common.<sup>2</sup> Perianal fistulas have also been reported in mixed-breed dogs.<sup>2</sup> The onset of the disease is typically in adult dogs. A sex predilection is not seen between male and female dogs, but intact male dogs are overrepresented.<sup>3</sup>

Proposed pathophysiology of perianal fistulas include anatomic confirmation theory and local T-cell mediated inflammation. The anatomic confirmation theory is based on the anatomy of the German Shepherd dog. This proposed that a low tail carriage causes an increase in irritation and moisture leading to bacterial growth of the perineum. This theory has fallen out of favor due to comparison of anatomic features of the predisposed breeds and the lack of bacterial growth associated with the sinus tracts.<sup>2</sup>

The local T-cell mediated inflammation theory is based on histopathology of the sinus tracts showing perivascular aggregation of CD3+ T lymphocytes within the lesions of dogs diagnosed with perianal fistulas. It is also suggested that type 1 helper T cells abnormally activate macrophages around the lesion progressing to development of the sinus tracts.<sup>2</sup>

Genetic associations have been explored in the German Shepherd dog. In particular, those from the United Kingdom and Finland have been associated with the class II MHC allele DLA-DRB1\*00101.<sup>1,3</sup> When homozygous for this allele, German shepherd dogs may develop perianal fistulas at less than 8 years of age. There is also a potential association between the CTNND2 gene found in affected and unaffected German shepherd dogs and the CTNND2 gene expressed in human Crohn's disease and ulcerative colitis patients suggesting a common pathogenesis between the 3 diseases.<sup>2,5</sup> However, fistulizing lesions of Crohn's disease are more commonly true fistulas with communication to the rectum. Both perianal fistulas and Crohn's disease demonstrate infiltration by type 17 T helper cells.<sup>2,10</sup>

### **Treatment and management options**

Previously, the treatment of choice for perianal fistulas was surgical excision of the draining tracts coupled with bilateral anal sacculectomy.<sup>7</sup> Recurrence of disease was noted in about half of cases as surgical management alone does not address the immune mediated component of the disease.<sup>2</sup>

The current standard of care is multimodal medical management that addresses the immune system, more specifically T-cells. Antimicrobial administration does not resolve the lesions but can be used to clear secondary infections of the draining sinuses. Cyclosporine A and tacrolimus are calcineurin inhibitors which bind intracellular protein cyclophilin-1 inhibiting calcineurin.<sup>8</sup> Ultimately decreasing cyclophilin-1 leads to the decreased production of IL-2 causing decreased activation and growth of T lymphocytes. Cyclosporine is used systemically whereas tacrolimus is best applied topically due to its lower molecular weight.<sup>2</sup> This allows better penetration of the skin. Cyclosporine has been proven to reduce lesion surface area and depth after 4 weeks with complete resolution of lesions as early as 16 weeks.<sup>6</sup> It is also

recommended to use the microemulsified formulations of cyclosporine A, which is more bioavailable in the dog. Cyclosporine dosing ranges widely but higher doses have been associated with better outcomes. Measuring cyclosporine A blood levels in the dog does not correlate with clinical response because cyclosporine is lipophilic and concentrates 10-fold higher in the dermis and epidermis; therefore, the dose should be tapered based on the clinical efficacy.<sup>8</sup> Common side effects with cyclosporine include vomiting, diarrhea, and anorexia. However, these clinical signs can be depressed by freezing cyclosporine for at least 30 minutes before administration and offering the frozen cyclosporine with a scant amount of food.<sup>8</sup> Use of anti-nausea drugs such as maropitant or metoclopramide as an antiemetic given two hours before the cyclosporine can decrease the adverse side effect of vomiting. Gingival hyperplasia and oral or cutaneous papillomas have also been reported with cyclosporine administration.<sup>8</sup> Cyclosporine is contraindicated in dogs with a history of malignant neoplasia.<sup>8</sup> Due to the expense and decreasing side effects, the dose of cyclosporine can be lowered by administering ketoconazole concurrently. Ketoconazole uses hepatic cytochrome P450 microenzyme to inhibit the hepatic metabolism of cyclosporine, resulting in higher blood levels. Ketoconazole also inhibits P-glycoprotein to decrease transport of cyclosporine into the lumen of the intestines and increases bioavailability of cyclosporine. Depending on the dose of ketoconazole used, the dose of cyclosporine can be decreased by at least 75%. Cyclosporine should be administered on an empty stomach.<sup>8</sup> Topical tacrolimus may be used alone to prevent relapse of perianal fistulas.<sup>2</sup>

Elimination diet trial using a novel protein or hydrolyzed protein diet is recommended but alone may not contribute to remission of perianal fistula. Studies have shown correlations between adverse food reactions, German Shepherd dogs, and perianal fistulas. Of the dogs in the study, 4 dogs had perianal fistulas, and all were German Shepherd dogs. Other studies found a

positive clinical response with fish and potato diets or venison and potato diets.<sup>2</sup> The diet change was in conjunction with other therapies such as metronidazole, tacrolimus 0.1% ointment, or prednisone.<sup>2</sup>

Mattis was diagnosed based on clinical presentation, although histopathology can be considered in atypical breeds or presentations. He was started on cyclosporine 150 mg every 12 hours for the resolution of the perianal fistulas. An Elizabethan collar was used to prevent Mattis from licking and biting the lesions, though it will not eliminate trauma potentially caused by other dogs in the house. Maropitant citrate was also prescribed to address the potential gastrointestinal side effects associated with cyclosporine. Mattis's ears were treated with Surolan otic suspension to address the yeast bilaterally and cocci in the left external ear canal. He was also prescribed cephalexin and prednisone to decrease the pruritus of the palmar and plantar aspects of his paws and to facilitate quicker healing of the perianal lesions. Because of his anxious behavior in the exam room and when away from his owner, Mattis was prescribed trazodone. Mattis was scheduled for a recheck examination in 2 weeks to evaluate his ears and perianal fistulas.

### **Case outcome**

Mattis presented on November 15, 2019, to recheck the perianal fistulas. The sinus tracts had begun to close. There was healthy, pink, granulation tissue. No exudation or debris was noted. On rectal examination, no stricture was evident. An estimated 20% - 30% improvement of the lesions was noted at this visit. Mattis presented for a second recheck on January 9, 2020. The perianal fistulas appeared to be continually healing with pink granulation tissue present bilaterally. The right side appeared more static than the left but had healed to approximately half

of the depth noted at initial presentation. The left side had reduced to a superficial slit like opening.

Mattis was lost to follow-up at Mississippi State University College of Veterinary Medicine after his appointment in January 2020.

Perianal fistulas should be a top differential in an adult German Shepherd dog with lesions of the perineum. Perianal fistulas are an immune-mediated disease; therefore, immunomodulating therapy such as cyclosporine should be preferred fist line therapy with clinical remission expected in approximately 16 weeks. Conjunctive therapy with ketoconazole, maropitant, and elimination diet trial will aid in decreasing the dose of cyclosporine and mitigating the adverse effects of cyclosporine. Dose reduction of cyclosporine should be based on clinical progression and not blood concentrations. In some cases, remission of perianal fistulas can be sustained with topical tacrolimus ointment without systemic immunomodulatory drugs. Historically, many affected dogs with perianal fistulas were euthanized but quick recognition of the clinical signs in predisposed breeds such as the German Shepherd dog and first line cyclosporine therapy can save many family pets.

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