

Freckles' Ill-fated Problem

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Introduction

Feline infectious peritonitis (FIP) remains a heartbreaking and frustrating disease in veterinary medicine today. FIP arises from a mutation of feline enteric corona virus (FCoV). FCoV infections are ubiquitous in the feline population and rarely cause significant disease, usually mild intestinal signs are observed.⁵ These infections are more common in crowded conditions, such as shelters and catteries. Only a small portion of cats with feline corona virus infections develop FIP, which is characterized by a pyogranulomatous vasculitis.¹ There are various factors that contribute to the development of FIP in these cats, including the virus itself, the host, and the environment.² Cats with FIP usually present younger than 1 year of age and the virus is a common cause of death in these young cats.⁵ The clinical signs of FIP are highly variable and depend on the immune system's response to the virus.² The most common form of FIP is the “wet” form, which is characterized by fluid accumulation in the body cavities. The “dry”, non-effusive form is much more variable, and signs depend on the organs or tissues involved. The following case report describes Freckles, a patient diagnosed with the non-effusive or “dry” form of feline infectious peritonitis. It will review history, presentation, pathophysiology, diagnostic approach, and treatment options of this disease process as well as the outcome of this patient.

History & Presentation

Freckles, an approximately 5-month-old male neutered Domestic Shorthair cat, was presented to the MSU CVM Community Veterinary Services on September 11th, 2020, for a wellness visit. Freckles was up to date on his vaccinations and kept indoor with one other cat. His owner reported that Freckles had a few episodes of diarrhea over the past two weeks and has looked bloated recently. She noticed that when she picked Freckles up, he seemed to be painful

in his abdominal region. She also stated that Freckles had been having signs of polyphagia, polyuria, and polydipsia at home. She also noticed that Freckles was more lethargic and not as playful as a kitten his age should be.

On presentation, Freckles was quiet, alert, and responsive. He weighed 3.8 kg with a body condition score of 6/9. His heart rate was 192 beats per minute, respiration rate of 48 breaths per minute, and his temperature was elevated at 104.7°F. His eyes and ears were clear of discharge and debris. His mucous membranes were moist and pink with a capillary refill time of less than 2 seconds. No crackles, wheezes, murmurs, or arrhythmias were appreciated on thoracic auscultation. His abdomen appeared to be slightly distended/ bloated and he was slightly painful cranially on abdominal palpation. All palpable lymph nodes were smooth, soft, and symmetrical. He was neurologically appropriate and had normal proprioception of all four limbs. There were a few small comedones and a mild amount of debris present along his bottom lip. All other aspects of his physical exam were within normal limits.

Pathophysiology

Feline corona virus belongs to the family coronaviridae which are large enveloped single stranded RNA viruses. RNA viruses are predisposed to high mutation rates due to a lack of proofreading ability. Cats with FCoV can be chronic carriers and shedders of the virus. With a prolonged disease course, there is more replication of the coronavirus particles. This chronic disease course sets up the perfect setting for mutation to occur and for a much more deadly form to occur. FIP viruses are able to spread systemically through their ability to replicate within monocytes and macrophages.^{2,7} As this replication occurs, the virus's ability to replicate within the enterocytes decreases, therefore, it is shed at low levels or not shed at all within the feces.² The majority of feline corona virus infected cats are healthy or only show mild intestinal signs.

FIP carries a much graver prognosis and rarely, if ever, results in the animal overcoming the disease. There are many speculated processes thought to occur in the development of feline infectious peritonitis and there have been many studies to try and better understand this disease process.

The cat's immune system plays a role in the development of FIP. It is believed that cats that mount a strong cell-mediated immune response are much less likely to develop FIP compared to cats that mount a greater humoral response.¹ In addition, stress is thought to play a role in the development of FIP. Cats in multi-cat households and overcrowding are at a higher risk of the development of FIP. These conditions may enable the rate of viral replication to be increased, thus increasing the chance for viral mutations and ultimately the development of feline infectious peritonitis.⁵

One of the mutations of the virus itself that has been shown to occur is a mutation in the spike (S) envelope glycoprotein gene.³ This surface protein is used in the attachment of the virus to its target cell, and ultimately the entrance of the virus into the host's cell.³ A mutation in this protein alone or in combination with other gene changes can promote the shift from feline corona virus to the more lethal feline infectious peritonitis.⁷

While the clinical picture of FIP can be quite variable between patients, there are two distinct manifestations of FIP. FIP is characterized by a vasculopathy that results in either protein-rich effusions in the body cavities or by pyogranulomatous lesions.^{1, 2, 7} Cats with both forms of FIP generally present with lethargy, fever that does not respond to NSAIDs or antibiotics, anorexia and weight loss.^{1, 5} The effusive form, also called the "wet" form, is generally thought to be more common in cats and the most common sign observed is ascites, although effusions can be seen in other body cavities as well.¹ Clinical signs with the non-

effusive form are more dependent on where in the body the infection is occurring. The “dry” form is most commonly associated with neurologic or ocular signs.^{1,2,5} Dermatologic signs, such as non-pruritic papules or nodules caused by pyogranulomatous-necrotizing phlebitis, can also be observed with FIP, however, these are less commonly reported.^{1,5}

Diagnostic approach

The diagnosis of feline infectious peritonitis ante-mortem is very difficult and may not be easily achieved without post-mortem histopathology. Often, the effusive form can provide an ante-mortem diagnosis as the effusions can be evaluated and obtained in relatively non-invasive manners.¹ Definitive diagnosis is traditionally made on histopathological examination of tissues with virus detection by immunohistochemistry (IHC) for feline corona virus antigens.⁵

Following Freckles’ initial exam, blood and urine were collected and submitted for analysis. The complete blood count (CBC) revealed a moderate regenerative left shift and microcytic normochromic anemia, with a PCV of 21%. His small animal profile (SAP) showed a moderate hyperproteinemia (10.6 g/dl; rr= 6.5-8.4), hyperglobulinemia (8.8 g/dl; rr= 4.1-6.0) and hypoalbuminemia (1.8 g/dl; rr=2.2-3.2). In addition, there was a mild hyperphosphatemia (6.6 mg/dl; rr=2.6-5.7) and hypomagnesaemia (1.5 mg/dl; rr=1.9-2.6). Urinalysis showed rare waxy casts and +3 proteinuria. The combination of Freckles’ clinical signs and his blood work findings, specifically hyperglobulinemia and hypoalbuminemia, heightened our suspicion that Freckles potentially was suffering from feline infectious peritonitis. After a discussion with Freckles’ owners regarding our top differential of FIP and its prognosis, they elected to monitor Freckles for worsening of clinical signs and to forgo abdominal radiographs, ultrasound, and further diagnostics. Freckles was sent home on a course of antibiotics in hopes that there could possibly be an underlying infection that the diagnostics performed at this visit could not identify.

Generally, hematological and serum biochemistry changes with FIP are non-specific and variable among patients.⁵ Often these patients will have a lymphopenia, a neutrophilia, a left shift and a mild to moderate normocytic normochromic anemia. A hyperglobulinemia is reported in many these cases, along with a hypoalbuminemia.⁵ In the effusive form, hyperbilirubinemia has been reported, often without elevations in alanine aminotransferase (ALT), alkaline phosphatase (ALP) or gamma-glutamyltransferase. Although these changes cannot themselves confirm that a cat is infected with feline infectious peritonitis, they can help to increase your suspicion and support the diagnosis.

Freckles returned on September 18th, 2020, for follow up blood work and abdominal imaging. At that time, Freckles was doing well at home, although he began to have an increasing frequency of the previously reported diarrhea and new signs of occasional vomiting. Freckles' bloodwork and urinalysis revealed similar findings compared to his first visit. On abdominal radiographs, the liver was enlarged with rounded margins, likely due to infectious etiologies. On abdominal ultrasound, marked lymphadenopathy, hepatomegaly and focally thickening of the small intestinal mucosal layer were appreciated. These changes were likely due to an infectious or inflammatory etiology such as granulomatous disease, though neoplasia could not be fully excluded at the time. There was also a trace amount of free fluid within the abdominal cavity; however, there was not enough fluid to collect a sample for cytologic examination.

In effusive forms, the effusions can often be collected and analyzed to help in the diagnosis of FIP. These effusions are usually clear, straw-yellow color, viscous and protein-rich.⁵ An inexpensive method of testing the effusion is the Rivalta test. This test is simple to perform and only requires a few common household products. To perform this test, 8mls of distilled water and one drop of acetic acid (vinegar) are mixed together.^{1, 5} A drop of the effusive sample

collected from the patient is dropped onto the surface of the mixture. A positive result retains its shape as it slowly falls to the bottom of the solution. This result is often described as having a “jelly-fish” appearance.¹ A negative result will dissolve into the solution as it is dropped in the mixture. While this test alone cannot diagnose FIP, it can help in ruling it out from your differential list. The Rivalta test is helpful in distinguishing transudates from exudates.^{1, 5} A positive result indicates the presence of an exudative effusion, not FIP itself. Effusive samples and tissue samples can be obtained and submitted for immunohistochemistry of FCoV antigen within macrophages and can be 100% predictive of FIP; however, a negative result cannot fully rule out FIP as effusive samples often have a low cellularity, thus a low number of macrophages present.^{1, 5}

As Freckles did not have enough abdominal fluid present to collect a sample, the Rivalta test could not be performed in his case. Biopsy and histopathology are necessary for the definitive diagnosis of FIP, which are often not obtainable unless they are collected post-mortem.^{1, 5} While changes in hematology and serum biochemistry are often non-specific in FIP cases, there are a few changes that are commonly reported.^{1, 5} Freckles bloodwork findings were supportive in our suspicion of FIP. Hyperglobulinemia is reported in approximately 90% of cases of FIP, while hypoalbuminemia is reported in approximately 65% of cases. Freckles also had a moderate left-shift microcytic normochromic anemia, which is also a common finding in cats with FIP.¹ While abdominal imaging did not reveal any obvious major lesions, they did support the likelihood of a potential infectious or inflammatory process occurring. Based on the diagnostics performed in this case and the lack of any substantial effusion within the abdominal cavity, it was presumed Freckles had the “dry” form of feline infectious peritonitis.

Treatment and Management

Unfortunately, there are no approved treatment options available in the United States for feline infectious peritonitis. Supportive treatment, usually with corticosteroids, aims at suppressing the immune response and inflammatory reactions.¹ Monitoring for quality of life is especially important in this disease process as most cats ultimately die.

Although the virus can live in the environment for extended periods of time, it is easily inactivated by most household cleaners.¹ Therefore, cleanliness is imperative in multi-cat households and crowded situations, such as catteries and shelters.

There is a potential treatment option that is available, although currently only on the “black market”. This drug is known as GS-441524, which is a nucleoside analog that inhibits viral replication. There have been several studies that have shown great promise for this drug in reversing the effects of FIP in cats and bringing them back to normal health.^{3,4} Currently, the only way to acquire this drug is through the “black market” which leads veterinarians at a crossroads due to legality concerns. Hopefully with future studies and successful cases, this drug can be evaluated via the proper channels required for approval and can provide veterinarians and owners with a potential treatment for this devastating disease.

Initially, Freckles was prescribed a course of antibiotics (Clavamox) in hopes that there was some underlying infection present. He had a few flare ups of diarrhea, so metronidazole was added to his treatment regime. This helped in improving his diarrheal signs; however, Freckles continued to slowly decline in health. He presented two more times to MSU-CVM’s Community Veterinary Service for constipation, which was medically managed with subcutaneous fluids and enemas.

Case Outcome

Freckles continued to have reoccurring bouts of diarrhea and occasional vomiting. Sadly, in January 2021, Freckles began exhibiting tachypnea. Due to concerns about effusion as the cause of the tachypnea and the decline in his quality of life, his owners elected human euthanasia and a necropsy was performed.

Necropsy revealed approximately 70-90 mls of yellow, slightly viscous fluid with numerous fibrin clots within the thoracic cavity. The lungs, internal thoracic wall and thoracic surface of the diaphragm were diffusely covered by a mat of fibrin. In addition, the lungs were severely atelectatic and the pericardial sac contained 1-2 mls of serosanguinous fluid. The epicardial surface of the auricles had multifocal granulomatous nodules. The liver was moderately enlarged with multifocal nodules present on the surface. Histopathology revealed a severe pyogranulomatous vasculitis of the vessels of the lungs, liver, and gastrointestinal tract. The combination of pleural effusion and multiple granulomatous lesions are common post-mortem findings in cases of FIP.⁵ In Freckles' case, a combination of the "dry" and "wet" forms of feline infectious peritonitis was confirmed. Cats with the "dry" form of FIP will often develop the "wet" form in the terminal stages as the immune system worsens during the progression of disease.⁷

Conclusion

In summary, feline infectious peritonitis is a complex disease process that has continued to be frustrating for veterinarians and owners. Historically, this disease carries a very poor prognosis with little hope for a recovery. There is now hope for veterinarians in providing a possible cure for FIP with the use of GS-441524. Hopefully with more research and more

successful cases, this drug can undergo the approval process and be available for veterinarians to provide for their future feline patients.

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