The Curious Case of George Banys

A Case Report of Feline Infectious Peritonitis

Joshua P. Bennett

Mississippi State University

College of Veterinary Medicine

Class of 2019

Clinicopathologic Conference

April 26th, 2019

Advisor:

Andrew Mackin, BSc, BVMS, MVS, DVSc, FANZCVSc, Diplomate ACVIM

Introduction

Feline Infectious Peritonitis (FIP) is a worldwide, fatal disease of felids caused by a feline coronavirus (FCoV). Despite first being described in the mid-1960's, FIP is one of the most prevalent and fatal infectious diseases of domestic cats.[4,2] Currently, there are two recognized feline coronaviruses known as feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV).[12] The FIPV is a mutant virus that originated from FECV, but other forms of FECV are not considered dangerous to cats, usually causing only subclinical or transient gastrointestinal disease in young cats.[3,4] There does not appear to be a breed or sex predisposition associated with FIPV.[2,3] These viruses are antigenically and morphologically indistinguishable from one another, which often make diagnosis difficult.[2] Mutations or recombinant strains of endemic FECV which are capable of FIP are thought to develop in the gastrointestinal tract of infected cats.[6]

Cats may become infected with the FIPV in two different ways, which include a mutation during FECV infection, or contraction from other cats with FIP, but this is rare.[2] The FECV is highly contagious and primarily contracted by ingestion of contaminated feces or saliva, however transmission by direct inoculation (cat bites, etc.) and in utero have been reported.[2,6] Infection is most common in crowded conditions (catteries, multiple cat households, etc.), while single cat households have a decreased prevalence.[1] Studies involving close cat colonies have demonstrated almost every cat becomes FECV infected.[6] In one study involving 155 naturally infected cats FECV viral RNA was found to be shed continuously (12%) and intermittently (28%) in the feces.[1,6] Some cats shed the virus initially and ceased shedding (36%) and a few were resistant to infection (3%).[6] Viral RNA can be shed in the feces of infected cats as early as 1-week post-infection and can continue to be shed for weeks, months, and a few for their entire

life (carriers).[1] FCoV's can survive up to 7 weeks in dry environments, but they are readily inactivated by most household detergents and disinfectants.[1]

Three different clinical manifestations of FIP have been reported, which include a wet (effusive) form, dry (non-effusive) form, and mixed form.[6] The most common non-specific signs produced by these forms are a fever that is not responsive to antibiotics, lethargy, anorexia, and weight loss.[1] The wet form of disease is an immune complex vasculitis characterized by a fibrinous polyserositis.[2,6] This leads to a leakage of protein rich fluid into the peritoneal cavity, pleural space, pericardial space, and subscapular space of the kidneys.[6] This can cause of variety of clinical signs, but most commonly dyspnea or a distended abdomen (ascites) are observed.[3] The dry form of disease forms pyogranulomatous or granulomatous lesions which can affect many different tissues, but most commonly the eyes, brain, kidneys, omentum, and liver.[6] A wide range of clinical signs is seen with the dry form depending on which tissues are affected. For example, renal involvement may lead to renomegaly which is detectable on palpation or, if mural lesions are present in the colon or ileocolic junction, then chronic diarrhea or vomiting may be observed.[1] The mixed form of disease is characterized by the development of both wet and dry lesions in the body.[6]

The antemortem diagnosis of FIP is often difficult, especially for the non-effusive form, and is usually a presumptive diagnosis based on a combination of clinical signs and clinicopathologic data. Currently the only ways to obtain a definitive diagnosis are through histopathology or demonstration of the virus in effusions or tissues by immunohistochemical staining.[6] The most accurate technique available detects the N-protein of the virus through immunohistochemistry of biopsy samples.[3] While FCoV may be present systemically in some healthy cats, only FIP cases will contain enough viral antigen in macrophages to result in a

positive staining.[1] Immunohistochemistry has been demonstrated to have a positive predictive value of 100% in FIP cases.[1] However, there is a wide range of tests that can be performed to support the diagnosis of FIP, most of which can only be utilized with the wet form of disease. Hematology commonly will display a lymphopenia, non-regenerative anemia, hyperglobulinemia (mainly gamma globulins), decreased albumin/globulin ratio, and increased liver or kidney enzymes.[1,10] Hyperglobulinemia has been found in around 50% of cats with the wet form and 70% of cats with dry form.[1] If effusion is present, it is typically clear yellow color with a viscous consistency with high protein content (>35 g/L) and low cellularity (<5,000 nucleated cells/mL).[1] Electrophoresis has a high positive predictive value if albumin/globulin ratio is <0.4 and high negative predictive value if >0.8.[1] Rivalta's test may be performed on effusions to differentiate between transudates and exudates with a positive predictive value of 86% and negative predictive value of 96%.[1] FCoV antigens are frequently detected in effusions by immunofluorescence and are not found in effusion caused by other diseases.[6] Additionally, viral RNA may be detected by reverse transcription polymerase chain reaction in effusions and is unlikely to be in effusions of other diseases.[6] Detection of serum antibody titers is of limited benefit to the diagnosis of FIP because infection by any FCoV can cause a cross-reaction to occur. [6,9]

History and Presentation

George Banys, a 2-year-old male neutered domestic short-haired cat, presented to Mississippi State University College of Veterinary Medicine Internal Medicine Department on January 31st, 2019 for a history of acute blindness and neurologic signs (ataxia). Three weeks prior to presentation, a red spot was discovered in his left eye. He was taken to his primary veterinarian the following day for evaluation and was prescribed neomycin and prednisolone

drops in both eyes (OU) for a fibrin clot in his left eye (OS) and a 2-week course of oral clindamycin. During this visit, a blood sample was collected for a complete blood count (CBC) and a feline viral panel. The CBC revealed a mildly decreased mean corpuscular hemoglobin (11.4 pg) and reticulocyte hemoglobin concentration (12.4 pg) with a mildly increased red cell distribution width (28.3%), mild leukocytosis (17.75 K/µL), mild monocytosis (0.89 K/µL), and moderate neutrophilia (14.46 K/µL). The feline viral panel was negative for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) but showed a positive antibody titer (greater than or equal to 1:12,800) for FCoV by immunofluorescence assay (IFA). George's ocular signs continued to progressively worsen, despite treatment, until both eyes became affected. Two days prior to presentation, his owners observed him having trouble entering/exiting the litterbox and navigating stairs in the home, specifically with his left hindlimb. He was taken to a primary veterinarian again and upon evaluation was found to be ataxic in his left forelimb and hindlimb with absent conscious proprioception. At the time of referral, this had progressively worsened and eventually all four limbs were affected.

On presentation, George was quiet, alert, and responsive. He weighed 3.8 kg and was determined to have an ideal body condition with a body condition score of 4/9. His vital signs were all within normal limits, including: a temperature of 99.9°F, pulse of 192 beats per minute, and respiratory rate of 32 breaths per minute. He had a mildly prolonged skin tent and his mucous membranes were pale pink and tacky with a capillary refill time of less than 2 seconds. Based on these results he was determined to be approximately 7-8% dehydrated. Grossly, both of his eyes appeared buphthalmic and further examination revealed fibrin in the anterior chamber and posterior synechia (OU). An enlarged bladder was present on abdominal palpation, but it was easily expressed. The remainder of his physical examination was unremarkable.

Diagnostic Approach/Considerations

Based on George's physical examination findings and previous laboratory data from the referring veterinarian, a rule out list was composed of several infectious etiologies (FIP, toxoplasmosis, cryptococcus, and histoplasmosis), neoplastic etiologies (lymphoma), and systemic hypertension. A full diagnostic plan was recommended to the owner, including complete bloodwork, urinalysis, blood pressure readings, head and neck magnetic resonance imaging (MRI) with cerebrospinal fluid (CSF) tap, and *Toxoplasma* titers. However, due to financial constraints, this was declined. A blood sample was collected for a chemistry panel which revealed a moderate hyperproteinemia (9.5 g/dl), a mild hyperglobulinemia (6.8 g/dl), and a moderately elevated creatinine kinase (913 U/L).

After examination of the CBC results, our primary rule-out was FIP, and working inside our financial constraints we elected to schedule Ophthalmology and Neurology consultations with Mississippi State University College of Veterinary Medicine Veterinary Specialty Center. The Ophthalmology consultation revealed buphthalmia, pupil mydriasis, superficial corneal ulcers, and slight direct and indirect pupillary light responses (PLR) in both eyes (OU). The right eye (OD) had 2+ aqueous flare, posterior synechia, and fibrin in the anterior chamber which was obscuring most of the pupil with blood in the anterior chamber. The left eye (OS) contained keratic precipitates (large aggregates of red and white blood cells) with fibrin deposited in the ventral anterior chamber and 3+ aqueous flare. The optic nerve had a cupped appearance and there were small pigmented lesions dorsal to the optic disc, which could be hemorrhage, but the view was distorted by the aqueous flare. A Schirmer Tear Test (STT) was normal in both eyes (15 mm per minute OD and 21 mm per minute OS). Fluorescein staining was positive (OU) and there was increased ocular pressure in both eyes (32 mmHg OD and 28 mmHg OS). Based on

these findings, George was diagnosed with superficial corneal ulcers (suspected cause is exposure keratitis), panuveitis, and glaucoma in both eyes. He was prescribed dorzolamide, ketorolac, and tobramycin with instructions for the owner to discontinue the prednisolone drops. His prognosis for vision long term was poor due to the presence of secondary glaucoma. The most likely rule-outs for these ocular signs included: FIP, lymphoma, toxoplasmosis, FeLV, and FIV.

The Neurology consultation revealed a nonambulatory tetraparesis and a normal mentation. Cranial nerve deficits discovered included: absent menace (OD) and decreased to absent menace (OS), absent following/tracking and pupillary light response (OU) and decreased to absent response to the sensory branch of the trigeminal nerve (CN V). The remainder of the cranial nerves were normal. Postural reaction deficits discovered included: decreased to absent wheelbarrowing, decreased to absent extensor postural thrust, absent hemiwalking in all four limbs, absent hopping in all four limbs, and absent conscious proprioception in all four limbs. Segmental reflexes were all normal and the remainder of the neurological examination was unremarkable. Considerations for the neurological deficits included: FIP, toxoplasmosis, rabies, *Cryptococcus neoformans*, FIV encephalopathy, bacterial meningitis or myelitis, and feline polioencephalomyelitis.

Pathophysiology

FECV that are capable of producing FIP are thought to develop in the gastrointestinal tract of some infected cats.[6] After entering the body, the virus infects lymphoid tissue in the gastrointestinal tract, specifically macrophages.[12] Infected monocytes and macrophages are critical in the ability of the virus to cause viremia and disseminate throughout the body.[1,6] Then, the upregulation of major histocompatibility complex II results in the activation of endothelial

cells by releasing cytokines and adhesion molecules to produce vasculitis.[5,12] The ability of FECV to induce proliferation and activation of macrophages and monocytes is mediated by the virus's ability to infect circulating monocytes.[5] It has been suggested that the activation of circulating monocytes may play a role in the development of vasculitis too.[12]

The development of FIP is thought to be determined by both viral genetics and host immunity.[1] Concurrent disease such as FeLV, respiratory disease, and FIV has been associated with an increase risk for developing FIP, suggesting that the immune system plays a critical role.[1,12] The presence of lesions has been associated with T and B cell depletion along with down regulation of IL-12.[1,5] It has been proposed that the down regulation of IL-12 might be responsible for impaired cellular immunity and failure to reduce or limit the viral load as seen with FIP.[5] Studies have suggested that a strong T cell-mediated response is seen in cats that do not develop FIP and cats showing a primarily B cell or humoral response progress to disease.[1] It has been proposed that humoral immunity may even enhance development of the wet form of disease.[12] This is thought to occur by two mechanisms: virus-antibody-complement complexes result in inflammation around blood vessels or antibody-dependent enhancement which involves the uptake of these complexes by macrophages followed by significant viral replication (only demonstrated experimentally).[12]

The effusive and non-effusive forms of FIP both demonstrate pyogranulomatous inflammation, leading to vasculitis and vascular necrosis resulting in infarction.[12] Wet FIP is characterized primarily by a serositis, resulting in fluid accumulation, with varying degrees of inflammation.[12] Dry FIP forms pyogranulomatous or granulomatous lesions which can affect many different tissues, but most commonly the eyes, brain, kidneys, omentum, and liver.[6] A recent study has demonstrated three distinct distributions of neuropathologic lesions in the CNS,

including leptomeningitis with superficial encephalitis, rhombencephalitis, and periventricular encephalitis (frequently the fourth ventricle).[8,12] Additionally, vasculitis in the CNS tends to affect blood vessels of the leptomeninges more frequently in sulci, near entrances to adjacent CNS tissues, and around the circle of Willis.[12]

Treatment and Management

Unfortunately, in most cases FIP is fatal within days to weeks of diagnosis, however there have been rare cases reported of cats surviving several months after diagnosis.[1,6] All cats with FIP should receive supportive care, which usually consists of providing good nutrition, minimizing stress, and broad-spectrum antibiotics that may be required for secondary bacterial infections.[3] The current treatment of choice is corticosteroids, most commonly prednisolone or dexamethasone, which could possibly have a link to prolonged remission in cats.[1,6] Treatment with corticosteroids is controversial, especially at immunosuppressive doses, since it has been suggested that cats with strong cell-mediated immune response do not develop FIP.[1] It has been suggested that an ideal treatment for FIP would include elimination of the virus combined with B lymphocyte suppression and the stimulation of T lymphocytes.[6] Historically, several different drugs aimed at inhibiting viral replication have been tested, including ribavirin, vidarabine, human interferon-α, feline fibroblastic interferon-β, adenine arabinoside, amphotericin B, and protease inhibitors (GC376), however none have been successful in curing FIP and most have severe side effects.[1,6,10] However, recently a nucleoside ribose analog, GS-441524, that has demonstrated potent antiviral activity against several RNA viruses displayed efficacy against FIP both *in vitro* and *in vivo*.[7,11] In one study, 25 out of 26 cats treated for 12 weeks or longer were able to achieve sustained remission (44 weeks at the end of the study) and the one death was suspected to be due to unrelated heart disease found at necropsy.[11] GS-441524 was determined to

be surprisingly non-toxic at the therapeutic dosages used in both studies.[7,11] Due to the progressively fatal nature of FIP, humane euthanasia should be considered once a patient starts to physically deteriorate and have a decreased quality of life.

Since there is currently no effective treatment approved by the Food and Drug Administration (FDA) for FIP, prevention is the mainstay in controlling disease. This is best accomplished by avoiding exposure to FCoV by maintaining good sanitation practices (cleaning litterbox regularly, disinfectants, etc.), isolating cats that may be shedding the virus, and keeping kittens and their queen isolated from other cats.[1,3,6] In households that previously had a cat diagnosed with FIP, it is recommended that they not introduce a new kitten into the environment for at least 2 months to allow the virus in the environment to die.[1] There is one commercially available vaccine currently on the market, however data concerning its efficacy is lacking.[1] It is not likely to be protective in cats that have previously been exposed to FCoV, and is only indicated in cats that have not been previously exposed to the virus.[6] It is not currently recommended by the American Association of Feline Practitioners.[6]

Case Outcome

After obtaining the results from the chemistry panel, Neurology consultation, and Ophthalmology consultation, George's owner was informed that the most likely diagnosis was FIP. Unfortunately, due to financial constraints and a poor prognosis, they elected to stop further diagnostic testing and treatment. George was discharged, and the owner took him home for humane euthanasia at his primary veterinarian the following day.

Prior to euthanasia at his primary veterinarian, the owner signed consent for a necropsy to be performed post-mortem. The primary veterinarian harvested several organs for

histopathology, which included the left eye (OS), lung, kidney, liver, spleen, pancreas, small intestine, and urinary bladder. The samples were sent to Mississippi State University College of Veterinary Medicine Diagnostic Laboratory Services for evaluation. Histopathology revealed multifocal pyogranulomatous and plasmacytic vasculitis of the kidney, multifocal pyogranulomatous and plasmacytic vasculitis with pulmonary edema and pyogranulomatous and fibrosing pleuritis in the lung, multifocal mild random pyogranulomatous hepatitis with lymphoplasmacytic cholangitis of the liver, and multifocal pyogranulomatous and plasmacytic iridocyclitis with vasculitis and optic neuritis of the left eye (OS). The sections of spleen, pancreas, small intestine, and urinary bladder were unremarkable. The histopathological findings of the affected organs resulted in a definitive diagnosis of multiorgan FIP (dry form).

References

1. Addie D, Belak S, Boucraut-Baralon C, Egberink H, Frymus T, Gruffydd-Jones T, Hartmann K, Hosie MJ, Lloret A, Lutz H, Marsilio F, Pennisi MG, Radford AD, Thiry E, Truyen U, and Horzinek MC. Feline Infectious Peritonitis ABCD guidelines on prevention and management. Journal of Feline Medicine and Surgery 2009; 11:594-604.
2. Gelbery HB. Alimentary System. In: McGavin DM, Zachary JF, eds. Pathologic Basis of Veterinary Disease. 4th ed. St. Louis: Mosby Elsevier, 2007; 380-382.
3. Johnson LR. Feline Enteric Coronavirus and Feline Infectious Peritonitis. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine. 7th ed. St. Louis: Saunders Elsevier, 2010; 3708-3810.
4. Kipar A, Meli ML. Feline infectious peritonitis: still an enigma? Veterinary Pathology 2014; 51:505-526.

5. Kipar A, Meli ML, Failing K, Euler T, Gomes-Keller MA, Schwartz D, Lutz H, and Reinacher M. Natural feline coronavirus infection: Differences in cytokine patterns in association with the outcome of infection. Veterinary Immunology and Immunopathology 2006; 112:141-155.
6. Lappin MR. Infectious Diseases. In: Nelson RW and Couto CG, eds. Small Animal Internal Medicine. 4th ed. St. Louis: Mosby Elsevier, 2009; 1281-1388.
7. Murphy BG, Perron M, Murakami E, Bauer K, Park Y, Eckstrand C, Liepnieks M, and Pedersen NC. The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies. Veterinary Microbiology 2018; 219:226-233.
8. Rissi DR. A retrospective study of the neuropathology and diagnosis of naturally occurring feline infectious peritonitis. Journal of Veterinary Diagnostic Investigation 2018; 30:392-399.
9. Soma T, Saito N, Kawaguchi M, and Sasai K. Feline coronavirus antibody titer in cerebrospinal fluid from cats with neurological signs. The Journal of Veterinary Medical Science 2018; 80:59-62.
10. Pedersen NC, Kim Y, Liu H, Kankanamalage ACG, Eckstrand C, Groutas WC, Bannasch M, Meadows JM, and Chang K. Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis. Journal of Feline Medicine and Surgery 2017; 20:378-392.
11. Pedersen NC, Perron M, Bannasch M, Montgomery E, Murakami E, Liepnieks M, and Liu H. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats

with naturally occurring feline infectious peritonitis. Journal of Feline Medicine and Surgery 2019; 21(4):271-281.

12. Zachary JF. Nervous System. In: McGavin DM, Zachary JF, eds. Pathologic Basis of Veterinary Disease. 4th ed. St. Louis: Mosby Elsevier, 2007; 883-885.