CHAPTER 75

Feline Infectious Peritonitis

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Overview

Feline infectious peritonitis (FIP) is one of the more common fatal diseases of young cats obtained from shelters and catteries. It is caused by the FIP virus (FIPv), which is the virulent form (biotype) of feline coronavirus (FCoV). The nonvirulent biotype of FCoV is the feline enteric coronavirus (FECV), which is found commonly in healthy cat populations worldwide (see Chapter 73). Although the FIPv can be inoculated into naïve cats using infected tissue extracts or fluids, it is infrequently transmitted horizontally. It is strongly cell and tissue bound so transmission via urine and feces occurs only when a lesion is adjacent to renal collecting ducts or the intestinal wall. The FIPv occurs as two serotypes, type I and type II. Type I is more common in Europe and the Americas, and type II is more prevalent in Asia.

The FECV mutates to become the FIPv, and it appears that this mutation primarily involves loss of the ORF 3c gene or the S gene, which results in a change in cell tropism from apical bowel epithelium to macrophages; however, new information suggests that the 3c and S genes may not solely be involved in the mutation. The mutation is more likely to occur during the primary illness phase and in kittens because of rapid FECV replication in both and reduced resistance of kittens. Although considered primarily enterocyte bound, the FECV has a brief systemic phase during primary infection, an important event that affects testing. Initially, it was thought that immunity to FECV infection did not result in immunity to FIPv, but the degree of cross-protection that occurs is primarily related to the relatedness of the FECV and FIPv strains involved. If they are extremely close, there is significant protection, and if they are distant, there is no protection.

The FIPv binds to the surface of a single peritoneal-type macrophage, becoming internalized into that cell. Transmission progresses from macrophage to macrophage and not as free virus in the blood. Virus-infected macrophages spread the infection to other organs. Infected macrophages in cats that will eventually develop FIP cause suppression of the cat's natural immunity through a form of signaling. This suppression does not occur in cats that are resistant to the development of FIP.

Many cats have a natural resistance to FIP. It increases with age and cannot be explained by simple genetic differences but rather through a polygenetic process. Inbreeding appears to be one of the most important genetic causes of decreased resistance to FIP. However, FIP resistance (immunity) is not always long term; some cats become susceptible after initially developing resistance.

Up to 20% of cats with FECV infections experience virus mutation. However, only a very small number of these mutant viruses produce clinical disease due to a strong and rapid cellular response. Cats that develop FIP have FIPv that can replicate at will within macrophages, leading to dissemination to cells throughout the body.

If strong cellular immunity occurs shortly after infection, virus replication is checked, and disease does not occur. If humoral immunity occurs without concurrent development of cellular immunity, effusive FIP results. Effusive FIP results when strong humoral immunity occurs with weak cellular immunity. It may begin with a transient episode of effusive FIP, progress to typical granuloma formation, and then become effusive again terminally as the immune system collapses. Noneffusive FIP occurs when there is an intermediate cellular response to the virus.

FIP is found where the FECV is found, which is in virtually all shelters, in nearly all catteries with more than six cats, and in 60% or more of multicat households. FECV infection occurs by the fecal-oral route with viral shedding occurring within a week of exposure. Shedding may persist for 18 months or more, be persistent for 4–6 months followed by intermittent periods of shedding, or the virus may be cleared within 6–8 months. However, reinfection resembling primary exposure often occurs. Virus shedding is roughly proportional to coronavirus antibody titers. Cats with titers of ≥ 1:100 are more likely to shed virus than those with titers ≤ 1:25.

The typical FIP fatality is 4–16 months of age; FIP is uncommon in cats over 3 years of age. Losses generally occur as isolated events within a given location (cattery or shelter). They are usually sporadic, unpredictable, and infrequent. Every cattery with sporadic FIP is likely to have more deaths if enough kittens are bred over a long enough period. The longer kittens are held before adoption, the greater the risk. After about 3 years of FIP losses, the disease tends to diminish due to population resistance. Although some breeds seem to be predisposed to FIP, the disease is more likely related to blood lines than to specific breeds. Rarely, FIP losses occur as an epizootic event with many deaths in succession; however, this pattern typically does not last more than 12 months. Epizootics are usually associated with population stresses, such as overcrowding, kitten explosions, adverse genetic concentration, or the introduction of a new strain of FECV.

There are two forms of FIP, effusive ("wet" or non-parenchymatous) and non-effusive ("dry" or granulomatous or parenchymatous). Only rarely do both occur simultaneously, and then it is usually during a transition from one form to the other. The wet form is most common; it involves the visceral serosa and omentum or the pleural surfaces. See Web Figure 75.1. Uncommonly, fluid will collect in the scrotum. See Web Figure 75.2. The dry form involves abdominal organs (notably kidneys, liver, mesenteric lymph nodes, and bowel wall; see Web Figure 75.3a to c), the central nervous system (CNS), and the eyes (see Web Figure 75.4). This form produces no inflammatory exudation into body cavities but causes granuloma formation. The inflammatory lesions begin at the organ surface and expand into the parenchyma of the organ.

The time from infection to disease of the effusive form is up to 2 weeks under experimental conditions and several weeks longer for the noneffusive form. Incubation time is unknown in natural infections, but there is evidence that subclinical disease may smolder for months or even years before the onset of overt disease, as FIP may occur following a long history of vague illness or poor growth. Thus, the early signs of FIP include progressive lethargy, intermittent fever, poor appetite, and weight loss.

As the disease becomes more clinically evident, lethargy and fever may become consistent, and appetite suppression and weight loss may become more progressive. The effusive form manifests itself as either abdominal distension due to ascites (see Web Figures 75.5a and b, and 75.6) or (less commonly) dyspnea due to pleural effusion (see Web Figures 75.7 and 75.8). Uncommonly, pericardial effusion occurs with or without pleural effusion. See Web Figure 75.9a to c. Ocular and CNS involvement occur in less than 10% of cats with effusive FIP. The most common ocular presentation is uveitis (see Web Figure 75.4); some cats

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experience an iris color change. See Web Figure 75.10. CNS signs include posterior paresis, incoordination, hyperesthesia, seizures and palsy of the brachial, trigeminal, facial, and sciatic nerves, hydrocephalus (See Web Figure 75.11), dementia, personality changes, nystagmus, head tilt, and circling. See Web Video 75.1. Polyarthritis due to generalized synovitis occurs frequently. The noneffusive form produces CNS or ocular disease in about 60% of affected cats, and signs related to specific organ failure may predominate.

Specific stresses of young cats are often correlated with on onset of FIP. These include pregnancy, parturition, spaying, neutering, and declawing. If these occur concurrently with FIPV challenge, they may be enough to tip the balance in favor of the virus at the host's expense.

Diagnosis

Primary Diagnostics

- Combination Testing: Because there is not a single, simple consistently diagnostic test, diagnosis is based on an accumulation of factors.
  - A young cat from a shelter or cattery with most of the following:
    - Uveitis.
    - CNS signs.
    - Elevated serum proteins.
    - Hyperbilirubinemia/hyperbilirubinuria.
    - Increased serum globulins and decreased serum albumin resulting in an A:G ratio < 0.6.
    - A fever that is not antibiotic responsive.
    - Lymphopenia, especially if accompanied by neutrophilia.
    - A non-regenerative anemia.
  - The odds of effusive FIP are high with the following:
    - A young cat from a shelter or cattery.
    - The laboratory findings as mentioned previously.
    - Yellow-tinged, mucinous, inflammatory ascites or pleural effusion without bacteria; occasionally it will be green-tinged. Touching a drop on a slide with a needle and pulling away will usually produce a string of fluid. See Web Video 75.1. A stained slide will have a purple background color due to the high protein content. See Web Figure 75.12, Web Video 75.1, and Chapter 291.
- Immunohistochemical examination of cells in the fluid will be positive for viral antigens and is confirmatory for the presence of the FIPv. However, the presence of the FIPv is not necessarily equivalent to clinical FIP.
- Radiographs and Ultrasound: Radiographs or an ultrasound study of the chest (See Web Figures 75.8 and 75.9a to c) and abdomen (See Web Figure 75.6) may reveal pleural effusion, pericardial effusion, or ascites. However, it is rare to have fluid in the chest and the abdomen simultaneously.
- Histopathology: This is considered confirmatory when it reveals pyogranulomas in a cat with appropriate clinical, hematological, and serological findings. See Web Figure 75.13.

Secondary Diagnostics

- Aqueous Humor: The presence of increases in proteins and leukocytes is consistent with noneffusive FIP.
- Renal Ultrasound: The kidneys are frequently the location of FIP lesions. The presence of small masses (granulomas) in the parenchyma (see Web Figure 75.3a to c), renomegaly (measuring 5+ cm longitudinally), and a medullary rim sign (see Web Figure 75.14) are strongly suggestive of noneffusive FIP.
- α_1-Acid glycoprotein (AGP) has been used as an indicator for FIP. It is said that in cats with suggestive clinical signs AGP levels of 1.5–2 μg/ml could discriminate cats with FIP and levels > 3 μg/ml were highly suggestive of FIP regardless of clinical signs. This is still very controversial.
- The Rivalta test has been used for many years to identify the presence of a high protein level (due to eight acute phase proteins), fibrinogen, and inflammatory mediators. However, the test is not specific for FIP and is only specific for the presence of inflammation.
- Cerebrospinal Fluid (CSF): This often shows increases in proteins (> 200 mg/dl) and leukocytes (> 100 cells/μl, consisting predominantly of neutrophils) when noneffusive FIP is present.
- FCoV Antibody Tests (Titers): These can be helpful but not diagnostic because they are produced by both the FECV and FIPv. Although titers > 1: 1600 are usually found in cats with FIP and negative titers are usually consistent with an FIP rule out, overlap is so great between the two groups that this test offers little definitive diagnostic value in individual cats. Additionally, the test may become negative in terminal FIP cats. *Do not diagnose FIP in an asymptomatic cat solely based on a positive FCoV titer regardless of the degree of elevation.*

Diagnostic Notes

- FCoV antibody titers may fall dramatically in the dying cat, especially with effusive disease. It is not unusual for these cats to have a negative FCoV titer.
- Antibody titers to the 7b protein are no more specific or sensitive than the direct immunofluorescent antibody (IFA) test.
- Tests for FIPv RNA based on the lack of the 7b gene (supposedly to identify the FIPv) are not specific enough to be diagnostic.
- If a coronavirus is confirmed in tissues or fluid of a cat with typical FIP signs, the virus is always an FIPv. If a coronavirus if found in the feces of a cat, healthy or not, it is always an FECV.

Therapy

Primary Therapeutics

- No treatment to date has proved consistently effective in curing FIP.
- Promising work is in progress on antiviral drugs and on drugs for treating human coronavirus disease.
- Polyphenyl Immunostimulant (www.sassandsass.com) is FDA approved for treating feline herpes infections. It has been used successfully in controlling some cases of noneffusive FIP. However, discontinuation of therapy results in rapid relapse.

Secondary Therapeutics

- Protease Inhibitor: GC376, a compound of the dipeptidyl transition state 3CLpro inhibitors, has been shown to reverse experimentally-induced effusive FIP within 20 days or less. Six of eight cats with clinical FIP returned to normal and remained normal for 8 months, the end of the study period. It does not appear to be successful if neurologic signs are present, and cats with ocular disease often progress to neurologic involvement and are then resistant to therapy. This experimental drug is not currently available commercially.
- Chloroquine, cyclosporine A, nonspecific immunostimulant drugs, antiviral drugs, other protease inhibitors, and other potential drug-targeted therapies are also being researched.

Therapeutic Notes

- Claims of successful treatment are usually based on spontaneous remissions or misdiagnoses.
- Discredited treatments include tylosin and prednisolone, prednisolone and phenylalanine mustard, prednisolone and cyclophosphamide, various immunosuppressive drugs, various immunostimulating drugs, including interferon, megadoses of vitamins, numerous nutraceuticals, and pentoxyfiline.

Cattery Control

- FCoV antibody testing should not be employed on asymptomatic cats because it does not answer the four important issues: (a) Is FIP present in any cat? (b) Is subclinical FIP present in any cat? (c) Will any given cat develop FIP in the future? and (d) Which cats are shedding FECV?
- Testing for FCoV in feces by PCR is not significant because it is a test for FECV. In a cattery or shelter environment it is nearly impossible to maintain an FECV-free facility with strict (and impractical) quarantine measures.

Prevention

- An FIP vaccine with significant efficacy has not been developed.
- Proper management can significantly reduce FIP incidence. The following must be avoided or minimized:
  - overcrowding
  - longer shelter stays
  - other kittenhood diseases, including panleukopenia and viral respiratory disease
  - breeding cats, especially toms, which have produced FIP kittens
  - inbreeding.
- A form of immunity develops over time. Closed populations will have a decrease in FIP over about 3 years.
- Strict isolation of queens and their kittens, weaning of kittens at 4–6 weeks of age, and continued kitten isolation until 16 weeks of age can prevent FECV infection and thus FIP. However, the elaborate quarantine measures required include separate quarters (i.e., another building), separate litter, food, and water pans, separate air space, and change-in/change-out protective clothing; measures of this nature are usually not feasible.
- The most cost-effective way to reduce FIP losses are:
  - Eliminate overcrowding. Have no more than six breeding queens.
  - Have proportionally more cats 3 years of age or older.
  - Reduce fecal-oral transmission by managing litter boxes, litter replacement, and microscopic and gross spread of litter and litter dust.
  - Select breeding stock carefully. Cull toms and queens that have produced FIP kittens.
  - Produce a minimum number of kittens each year.
  - Avoid inbreeding.

Prognosis

The prognosis for FIP is grave. Currently, euthanasia is the correct recommendation when the diagnosis is confirmed or reasonably confirmed.

Suggested Readings

Kim, Y., Liu, H., Galasiti Kankanamalage, A., et al. (2016) Reversal of the progression of fatal coronavirus infection in cats by a broad-spectrum coronavirus protease inhibitor. *PLoS Pathog* 12(3), e1005531.

Legendre, A.M., Bartges, J.W. (2009) Effect of Polyprenyl Immunostimulant on the survival times of three cats with the dry form of feline infectious peritonitis. *J Fel Med Surg* 11(8), 624–626.

Pedersen, N.C. (2009) A review of feline infectious peritonitis virus infection: 1963–2008. *J Fel Med Surg* 11(4), 225–258.

Pedersen, N.C. (2014) An update on feline infectious peritonitis: Virology and immunopathogenesis. *Vet J* 201(2), 123–132.

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Norsworthy's Notes

FIP is a disease with a grave prognosis, therefore one must diagnose it cautiously, especially if the kitten is from a cattery. Unfortunately, a confirmed diagnosis requires histopathology as currently there are no other confirmatory tests. The current tests attempt to confirm the presence of inflammation or the presence of the FIPv. Inflammation is not unique to FIP, and finding the FIPv does not confirm the disease FIP any more than confirming the presence of the feline immunodeficiency virus or the feline leukemia virus confirms disease caused by them.

Despite all the emphasis on finding a new confirmatory test, one must not get buried in details and fail to look at the big picture. Consider the source of the cat, the clinical signs, and laboratory findings. A tentative diagnosis is often the best one available antemortem, but that is often sufficient. The only significant differential I see in my geographic location is histoplasmosis; it can produce a confusing, look-alike disease compared to noneffusive FIP and can occur in cats less than 1 year of age.