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UPDATES IN FIP: PATHOGENESIS, DIAGNOSIS AND TREATMENT
Jacqueline Norris, BVSc (hons), MVSt, PhD, MASM, GradCertEduc (Higher)
Faculty of Veterinary Science, University of Sydney, Australia

Introduction

Feline infectious peritonitis (FIP) is a systemic disease induced by virulent mutant forms of Feline Coronavirus (FCoV) and is a major infectious cause of mortality in young cats. It occurs in cats of all ages but most commonly those under 3 years-of-age. Currently there is no effective prevention or treatment for FIP. Equally, there is no method of accurately predicting which cats are at risk of developing the disease. The invariably fatal consequences, lack of predictable disease patterns, ineffective treatment regimes and the significant emotional and financial impact of FIP makes it a formidable disease.

FCoV infection is common in cattery-confined cats (80-100%) and pet cats (20-35%) worldwide due to faeco-oral transmission and viral resistance, but the outcomes of infection are variable. Most cats infected with FCoV live their lives without consequence, while the development of the lethal disease FIP is an unusual consequence in a small % of cats (<5%). While there is widespread belief that FIP results from virulent FCoV mutants that develop during infection within an individual cat, there is mounting evidence that an individual cat’s immune response to FCoV and its ability to control FCoV replication in macrophages is an essential element in disease pathogenesis. Ongoing research characterising the protective immune responses of resistant cats and the immunopathogenesis of disease in susceptible cats is fundamental to the design of prevention strategies, breeding programs and therapy.

Pathogenesis

Significant shifts in our understanding of FCoV infection and FIP pathogenesis have occurred over time. Originally it was thought that most FCoV infections were localised to enterocytes and that systemic infection with FCoV was a defining moment in the development of FIP. Subsequently, systemic infection with FCoV has been found to be a common consequence of FCoV infection and in the most cases is subclinical. This systemic infection in naturally or experimentally infected cats occurs as the result of a monocyte-associated viraemia. Kipar et al (1999) showed that FCoV infection leads to increased numbers of monocyte/macrophages in haemolymphatic tissues whether FIP develops or not. The monocytes/macrophages remain key players in the development of FIP. They are essential in FCoV replication, formation of granulomatous lesions and development of vasculitis seen in FIP.

The recent emphasis of FIP research worldwide has been on the dynamics of the feline immune response. Most studies have focused on cats with FIP or experimentally infected cats. These cats often develop a profound T-cell depletion in peripheral blood and lymphatic tissues, coupled with hypergammaglobulinemia. These findings indicate a severe virus-induced
immune dysregulation in which the humoral immune response contributes to disease pathogenesis rather than being protective, while the down regulation of the CMI response allows uncontrolled viral replication. Despite an often marked humoral immune response, antibodies seem unable to recognise FCoV infected cells. Dewerchin et al (2006) determined that FCoV infected monocytes exposed to FCoV specific antibodies caused internalisation of viral proteins normally expressed on the cell surface, rendering the infected cell ‘invisible’ to the immune system. Groot-Mijnes et al (2005) monitored the immune response of cats that were experimentally infected with the highly virulent FIPV strain 79-1146. Initially, all animals developed fever, wt loss and lymphopaenia but could contain the infection. Total lymphocyte counts recovered with time; however, in most animals, the infection relapsed (increase viral load). Enhanced FIPV replication coincided with fever, wt loss, and a dramatic decline in peripheral CD4+ and CD8+ T-cell counts. In contrast, cats that survived infection with the highly virulent FIPV strain 79-1146 had CD8+ T cells that were activated against the spike protein S. They postulate that the efficacy of the initial T-cell responses critically determines disease progression and the ultimate outcome of the infection. Deepening our understanding of the nature of immune protection and the role of immune effector products in the control of FCoV infection and prevention of FIP is essential.

Diagnosis – Confirmatory, Supportive and Circumstantial Evidence

The difficulties in diagnosing FIP have been a hot topic in feline medicine for many years. Adopting traditional instruments of infectious disease diagnosis (eg PCR, serology) for FIP diagnosis and FCoV infection control has led to ongoing confusion for vets and unwarranted euthanasia of cats. This has stemmed from an incomplete understanding of the dynamics of FCoV infection in cats and the pathogenesis of FIP. Unfortunately, virulent variants of FCoV are antigenically and often genetically indistinguishable from other feline coronaviruses making it difficult to design diagnostic tests to identify them. Diagnostic tests for FIP must therefore rely on the biological behaviour of the virus. A key feature of the mutant FCoV is the ability to replicate prolifically in macrophages/monocytes and it is on this premise that the only reliable diagnostic tests for FIP are based. The diagnosis of FIP (correct or otherwise) often leads to euthanasia due to significant morbidity and lack of successful treatment options. The death toll has been enhanced by over reliance on scant circumstantial diagnostic evidence.

Confirmatory evidence of FIP

Histopathology remains essential for the diagnosis of FIP. The presence of fibrinous and granulomatous lesions on the serosal surfaces with protein rich effusions into body cavities, pyogranulomatous vasculitis/perivasculitis and/or variable distributed pyogranulomatous lesions within several organs of the body are considered diagnostic for FIP. This is frequently followed by immunohistochemistry, a more specific technique, now available in many places worldwide. This uses anti-FCoV antibody to identify FCoV within macrophages in formalin-fixed, paraffin-embedded tissues and is used
subsequent to histopathology to definitively confirm FIP. This technique only detects macrophages with sufficiently high numbers of FCoV.

Supportive evidence of FIP

Direct Immunofluorescence on abdominal/pleural/pericardial fluid: Together with a supportive fluid analysis (see below), the presence of FCoV positive macrophages in the abdominal/pleural/pericardial fluid is highly supportive of FIP (100% specific).7

Alpha-1- acid glycoprotein (AGP): is an acute phase protein that rises during infectious and inflammatory conditions. It is not specific for FIP. Duthie et al (1997) determined that levels >1.5 g/L in serum, plasma or effusions were highly valuable in distinguishing FIP from other diseases with similar clinical signs. Giordano and colleagues (2003) found that cats with FIP had AGP of 2.72 +/- 1.46 which was significantly higher than clinical normal SPF cats or FCoV exposed cats (AGP ~1.20 +/-0.6).

Albumin/globulin ratios in serum and effusion: Serum a/g ratio <0.8 has a high probability (92%) of FIP. Effusion a/g ratio <0.4 also has a high probability of FIP.

Circumstantial evidence of FIP

Convicting a criminal requires incriminating evidence directly linking them to the crime. In the absence of this, a significant body of circumstantial evidence would be required to quash ‘reasonable doubt’. The same philosophy should apply to FIP diagnosis.

Signalment: FIP can occur in cats of all ages but young cats frequently (~50% cases) less than 3 yrs old are significantly over presented in all studies worldwide. Some report an over-representation of male cats in FIP cohorts but this is not reported universally. Pedigree cats are over represented with certain breeds reported more frequently.8, 9

Clinical signs: Two broad forms of the disease have been described across all ages and breeds: ‘effusive’ and ‘non-effusive’. These divisions are not always distinct with some cats crossing over to the other during the course of disease. Typically, patients with effusive FIP have high protein peritoneal and/or thoracic effusion(s), fever, wt loss, anaemia and elevated serum globulin levels, although not all cats fit this stereotype. Non-effusive FIP is often more vague in its presentation with nonspecific signs including fever, wt loss, malaise and inappetence. Clinical signs, beyond the non-specific, relate to the tissues affected (liver, kidney, pancreas, spleen, abdominal LN, CNS, lung, GIT, eyes, skin, heart). Usually >1 body system is involved but occasionally only 1 is affected, most freq CNS or GIT (but necropsy may reveal pathology in other areas).

Haematology: Mild neutrophilia and lymphopaenia are frequently seen in cats with FIP but these are non-specific findings seen in many other diseases. Non-regenerative anaemia (HCT <30%) is a frequent finding (~65% cases). Fulminant haemolytic anaemia has been reported by some.8 Thrombocytopenia is also reported in end stage disease.

Serum Biochemistry: The distribution of lesions within organs is variable and so elevations of biochemical parameters reflecting this organ damage are similarly variable. Abnormalities in serum biochemical parameters may not be seen even when the pathology is significant. A common abnormality in serum
biochemistry is elevated total protein due to elevations in serum gamma-globulin. Remember this occurs in many other diseases other than FIP (eg periodontal disease, stomatitis, chronic URT infection, heartworm infection etc) and reflects chronic antigenic stimulation. If serum gamma globulin (determined by protein electrophoresis) is 2.5g/dL, specificity for FIP is 86%.7

Diagnostic imaging: A useful antemortem indicator of neurological FIP on MRI is periventricular contrast enhancement, ventricular dilatation, and hydrocephalus.13 The absence of these findings does not exclude FIP.

Serology: The measurement of anti-FCoV antibody titres is the most misinterpreted test in feline medicine. A serum antibody test for what was thought to be exclusively FIPV was first developed in 1976 to assist FIP diagnosis.10 The antibody test used monolayers of infected liver cells from kittens with FIP and so the assumption that only FIPV antibody titres were being measured was reasonable. Shortly after,11 many healthy cats were found with high antibody titres to ‘FIPV’ and the validity of the test was questioned. This was first thought to be the result of previous exposure and recovery from FIPV but it was soon realised that all FCoV were antigenically similar and could not be differentiated by serology. These tests were in fact detecting antibody titres to any feline coronavirus. The advent of the 7B FIP antibody test was similarly based on an incorrect premise and has/should be withdrawn worldwide.

The accepted method for measuring FCoV antibody titres is now indirect immunofluorescence (indirect IFA). However there is variation between labs in the method of IFA used. Some use porcine cell lines infected with TGE (pig coronavirus), some use feline cell lines infected with FCoV type 1 or type 2. This variation in method was originally thought to be unimportant but Kummrow et al (2005)12 confirmed an enormous difference in the FCoV antibody titres reached depending on the cell line and virus used. Labs must not use the commonly quoted titre of 1:1600 as being highly predictive of FIP (PPV 0.94; Hartmann et al, 2003) when the method used is not TGE and porcine cell based.

Cats with FIP often have very high serum coronavirus antibody titres. There is however an overlap in antibody titres with non-FIP cats and so must be interpreted with caution. It is not possible to accurately interpret high antibody titres in cats that have come from multicat households in the last 12 months (perhaps longer with some). Our research group commonly measures high antibody titres (1:1600-1:6400 using FCoV type 1 infected feline cells) in healthy cats from breeding catteries. In older cats from single cat households, measurement of FCoV antibody titre may be helpful in supporting a diagnosis of FIP but must never be used in isolation. In neurological cases, measuring the FCoV antibody levels in the CSF vs the serum can be useful.

PCR tests: The endemic nature of FCoV infection in many cat populations and the discovery that systemic infection with FCoV is seen in healthy cats makes this a dangerously sensitive tool. PCR cannot differentiate virulent FCoV mutants from other FCoV as there is no one site of the genome that is common amongst all mutants.

Fluid analysis (abdominal, pleural or pericardial fluid): In the effusive form of FIP, high protein (>35g/L) fluid may be present. This elevated protein is mainly due to increased concentrations of gamma globulin. If effusion gamma globulin (determined by protein electrophoresis) is 1.0 g/dL, specificity for FIP
is 83%. The fluid is typically low to moderate cellularity (2000-6000 cells/ul) with predominantly neutrophils and macrophages. In acute cases, the neutrophil population is frequently higher than macrophages with an increase in macrophage numbers increasing with chronicity. Rivalta’s test has PPV of 86% and NPV of 97%.

**CSF analysis:** Some suggest FIP can be differentiated from other causes of CNS disease when CSF shows protein level >2 g/L and neutrophilic pleocytosis but this is not always the case. Measuring the FCoV antibody levels in the CSF vs the serum can be useful. A ratio considerably above 1 is supportive of neurological FIP.

**Treatment**

Unfortunately no new exciting treatments to report here. Treatments proposed for FIP aim to either suppress the immune system’s attack on body tissues or enhance the body’s ability to limit viral replication. No treatments to date have done this with overwhelming success or for extended periods. However in some cases, the treatments have afforded the cat and owner several months of life of reasonable quality.

**Prednisolone:** 2-4mg/kg/day PO gradually reducing dose every 2 weeks until optimal dose is reached based on continued response to treatment while minimising side effects. Prednisolone suppresses humoral and cell mediated immunity. It does help to improve the cat’s quality of life and appetite for a variable length of time. Others use Cyclophosphamide 2 to 3 mg/kg 4 times weekly orally.

**Thalidomide:** (50 to 100mg per cat SID at night) aims to reduce inflammation and humoral immune response without affecting CMI. Tetragenic to owner and cats so beware

**Thromboxane synthetase inhibitors** (oragrel HCl) 5mg/kg BID: inhibits platelet aggregation and has been reported to improve clinical signs in some cats. **Pentoxiphylline** (Trental) (100mg per cat PO BID) is aimed at decreasing vasculitis and is often used with pred.

**Feline recombinant omega interferon:** (1M IU s/c EOD plus pred) there was great excitement with the results of a small uncontrolled trial in Japan (Ishida 2004) showing that a third of cases (4/12) enjoyed prolonged resolution of clinical signs. Success with this drug in the hands of others has been variable. In a recent randomised placebo-controlled trial by Hartmann and colleagues, 34 cats with FIP were treated with interferon-omega (1M IU s/c eod for 7 days then once weekly) or placebo. All cats were given glucocorticoids. There was no statistical difference in the two groups. Only 1 long term survivor was seen (>3mths) which was in the interferon group.

**References**

Available on request