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Feline Infectious Peritonitis

An Immune-Mediated Coronaviral Vasculitis

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Our understanding of the pathogenesis of feline infectious peritonitis (FIP) has improved dramatically in recent years. Patients with FIP apparently represent only a small fraction of cats infected with coronaviruses, because many cats in the general feline population have antibodies that cross-react with FIP virus (FIPV). Continuing investigation into the sero-epizootiology of FIPV has raised more questions than have been answered. *Do most strains of FIPV cause no more than a localized infection and a chronic asymptomatic carrier state? Are all strains of FIPV of equal virulence, with the immunologic response of the infected cat solely determining the eventual outcome?*

The objective of this article is to review the various factors predisposing cats to FIPV infection, and to clarify the immunopathogenetic mechanisms responsible for the development of clinical disease. In light of our present knowledge of FIPV and the basic pathologic lesions it induces in terminally ill cats, FIPV might more accurately be named *feline coronaviral vasculitis.*

FELINE INFECTIOUS PERITONITIS VIRUS

FIP is caused by a coronavirus. Coronaviruses are pleomorphic, enveloped particles that average 100 nm in diameter and contain a single strand of RNA.[3, 10] Characteristic petal-shaped projections called peplomers protrude from the viral surface.[20] In many species of animals, coronaviruses have a relatively restricted organ tropism, infecting the respiratory and/or gastrointestinal systems.[29] Following oral infection, the viruses have an affinity for the mature apical columnar epithelium of the villi in the duodenum, jejunum, and ileum.[24] Younger members of any species tend

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to develop overt signs of infection, whereas the asymptomatic carrier state is more common in adult animals. In the cat and mouse, however, coronaviral infections may involve several organs, and persistent and chronic diseases often occur in these two species.[29] Similar to other coronaviruses, FIPV replicates in enterocytes but uncharacteristically replicates in macrophages, budding from the endoplasmic reticulum. Tissues such as spleen, liver, and lymph nodes with extensive reticuloendothelial components are preferentially infected with FIPV.[32] Early investigations demonstrated that the tissue tropism, intracellular location, and budding characteristics of FIPV closely resembled those of mouse hepatitis virus, strengthening the suspicions that FIPV was a fellow member of the coronaviruses.[17]

FIPV is a heat labile virus, being inactivated at room temperature within 24 to 48 hours. Infectivity is destroyed by most household disinfectants and detergents[5] In organ homogenates, however, FIPV remains stable for many months at −70°C, resisting repeated freezing and thawing.[16]

PROPOSED PATHOGENESIS OF FIP

FIPV and Other Feline Coronaviruses

Complicating our understanding of the pathogenesis of FIP is the knowledge that cats are susceptible to infection with several coronaviruses.[2] By natural routes of inoculation, asymptomatic infections, mild gastrointestinal signs, or classical FIPV may result from infection. Certain isolates that cause intestinal lesions following intragastric inoculation induce fibrinous serositis when injected intraperitoneally.[8] To some degree, therefore, the distribution and extent of lesions in cats with naturally occurring FIP may depend on the route of exposure and the dose and strain of FIPV.[28]

Other coronaviruses, such as the feline enteric coronavirus (FECV), do not cause fibrinous peritonitis when injected intraperitoneally.[24] The FECV causes nonfatal enteritis in kittens 4 to 12 weeks of age.[1, 19, 24] The virus is widespread in the cat population and is enzootic in most multiple-cat households and catteries. The virus persists in recovered animals, many of whom remain continuous shedders.

FECV is highly infectious by the oral route and has an affinity, like many coronaviruses, for the apical columnar epithelium of the intestinal villi from mid duodenum to cecum.[19] Most adult cats undergo subclinical infections; however, low grade fever, vomiting, and diarrhea have been noted in recently weaned kittens. FECV is closely related antigenically to FIPV and cross-reacts with FIPV in the serologic tests presently used for the diagnosis of FIP. The relationship between these two viruses remains unclear, and FECV *may* represent a strain of FIPV that is avirulent for most cats.[25] As noted later in this article, primary infection of cats with FECV with development of coronaviral antibody may sensitize cats to later exposure by heterotypic coronaviruses capable of inducing disseminated disease.[24]

Gastrointestinal Infections with FIPV

Certain strains of FIPV cause enteritis and/or fibrinous serositis in kittens after intragastric inoculation.[7, 8] By this route of inoculation, fibrinous serositis was only observed in kittens that were seropositive at the time of challenge. Fibrinous serositis did occur, however, in seronegative kittens after intraperitoneal inoculation of the same viral strain.

Diarrhea occurs in both natural and experimental cases of FIP.[7] Extensive sloughing of small intestinal enterocytes with shortening and fusion of villi has been noted in naturally occurring FIP. Virus-specific fluorescence has been observed with enterocytes and mesenteric lymph nodes. Coronaviral-like particles have also been found in fecal samples from a natural case of FIP.[7] Necrotized and desquamated enterocytes also showed positive immunofluorescence. In addition, FIPV replicates in the absorptive epithelial cells of small intestinal organ cultures, releasing free virions into the culture medium.[11]

These studies suggest that fecal and oral transmission of FIPV may occur within the feline population. A carrier state might develop as a result of persistent infection of enterocytes.

Localization of Dissemination

Long-term exposure of kittens to daily low doses of FIPV in their food caused clinical disease in 20 per cent of cats.[23] Many kittens in this study failed to seroconvert, suggesting that their intestinal epithelium had an innate resistance to infection with that strain and dose of FIPV. From these observations, it was proposed that the development of clinical FIP might depend on an intrinsic susceptibility of the intestinal or respiratory tract epithelium to infection. Subsequent dissemination of virus and the development of clinical signs might further be dependent on an immune response that was nonprotective.[23]

Both the strain of FIPV and challenge dose of virus contacted by the susceptible cat may be critical at this point. With larger doses of virus, more cats become infected and the ratio of diseased to asymptomatic cats increases.[20]

Following *aerosol* exposure, initial localization and replication of virus beyond the epithelium occurs in large mononuclear cells in regional lymphoreticular tissue or in subepithelial layers. The initial target cells for FIPV may be the dendritic macrophage, located in the cortex of lymph nodes.[32] One can speculate that similar internalization of virus might occur through the intestinal epithelium following oral exposure.

Virus-macrophage interaction at this point may determine whether infection is localized to the intestinal or respiratory tract or becomes disseminated.[31] Genetic factors affecting the phenotype of the murine macrophage, as well as virulence factors for different mouse hepatitis virus strains (another coronavirus), influence the capacity of that virus to replicate in macrophages.[31] A similar situation *may* occur with FIPV, with some cats terminating dissemination at this point owing to effective virus inactivation. In other cats, replication in macrophages may go uncontrolled. Individual

susceptibility may also be critical at this stage of infection, because smaller, weaker kittens often react adversely to exposure to FIPV.

Cats that mount an effective cell-mediated immune response upon exposure to FIPV may be protected against viremia and clinical disease.[20] Cats capable of developing only a partial cell-mediated immune response may ultimately develop the noneffusive form of FIP, which may be considered a partially controlled or smoldering form of the disease. The intensity of inflammation and amount of virus is considerably less in lesions of noneffusive FIP, when compared to the effusive form. Activation of localized or dormant infections may occur if the cell-mediated immune responsiveness of cats is impaired by feline leukemia virus (FeLV) infection.[20]

The course of disease may now be influenced by the development of a nonprotective and deleterious humoral immune response.

Cell-Associated Viremia

Dissemination of FIPV appears to depend on the presence or development of antibody cross-reacting with the virus. Most cats with clinical FIP are seropositive, suggesting that detectable antibody is not protective in vivo.[2]

To the detriment of the infected cat, coronaviral antibody opsonizes FIPV, enhancing its uptake into macrophages. Because FIPV replicates preferentially in macrophages, antibody aids delivery of virus to susceptible tissues. A primary cell-associated viremia may result in subsequent infection of macrophages and reticuoendothelial cells in target organs such as liver and spleen, which contain extensive blood sinusoids.[32] Spread of infection to specialized macrophages in vessel walls and migration of infected mononuclear cells across the endothelium may result in early vascular and perivascular infection in liver and spleen.[32] Secondary viremia, with spread of virus to other tissues, may then occur.

Immune Complex Formation

In addition to the deleterious complications previously described, an exaggerated and nonprotective humoral response may result in antibody excess, causing the formation of large immune complexes that are rapidly phagocytized by the reticuloendothelial system.[32] Immune complexes deposited in small blood vessels fix and activate complement, resulting in the release of the third component of complement (C3). Phagocytosis of aggregates containing virus, immunoglobulin (Ig), and C3 is aided by the presence of receptors for Ig and C3 on the macrophage surface.[31]

Complement-Mediated Vasculitis

Macrophages in perivascular locations that ingest aggregates of FIPV, Ig, and C3 foster replication of virus, degenerate, and release new virus and complement components (some of which are synthesized in macrophages).[12] A vicious cycle of complement-mediated vascular damage ensues, resulting in release of chemotactic complement components and attraction of neutrophils. Release of proteolytic enzymes from degenerating neutrophils exacerbates tissue damage. In naturally occurring cases, degenerative

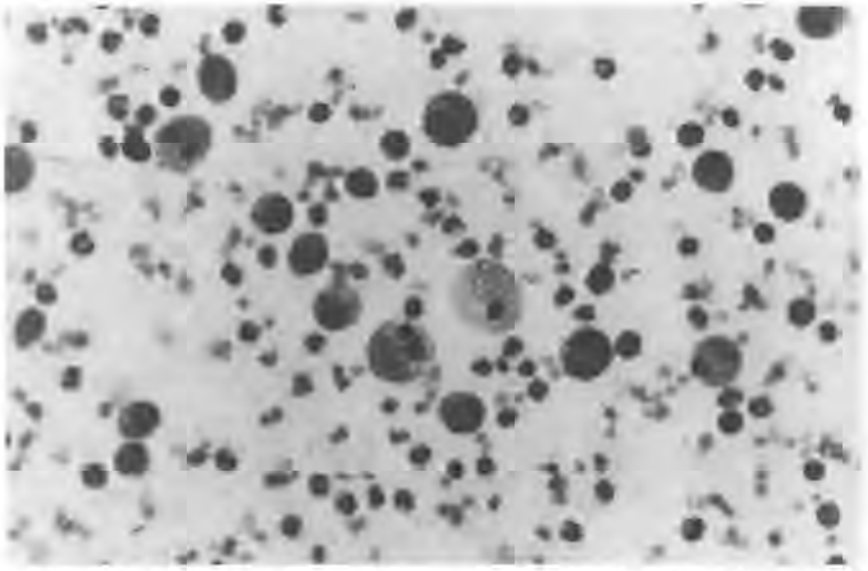

Figure 1. Nondegenerate neutrophils, macrophages, and erythrocytes in the exudate of a cat with effusive FIP. (Photograph courtesy of Dr. William Chickering, Virginia Tech.)

and proliferative changes occur in blood vessels, particularly in the endothelial and medial layers of small veins and arteries in the peritoneal and pleural serosa and in the interstitial connective tissue of parenchymatous organs.[6] The vascular lesion of FIP is an Arthus-type reaction, resulting in a pyoganulomatous inflammatory response.

In fulminant cases, complement-mediated damage to vascular endothelium results in increased vascular permeability and the outpouring of immunoglobulin- and fibrin-rich exudate found in effusive FIP (Fig. 1).

Coagulopathies in Fulminant FIP

Under experimental conditions, damage to the vascular endothelium, presumably from widespread immune complex deposition, produced multiple in vitro clotting abnormalities.[30] The development of thrombocytopenia, hyperfibrinogenemia, increased quantities of fibrin-fibrinogen degradation products, and depression of factors VII, VIII, IX, X, XI, and XII plasma activities suggested that disseminated intravascular coagulation might be an important terminal complication of FIP. Coagulopathies have been noted in naturally occurring cases of the disease.[5] Thrombosis and blood stasis in small veins may enhance seeding of virus and dissemination through vessel walls at these sites.[30]

Role of Sensitizing Antibody in FIP

As noted previously, antibody cross-reacting with FIPV influences both the outcome of infection and the course of disease. When compared to

seronegative kittens, experimental infection of coronaviral antibody-positive kittens results in the following:

1. Tendency for dissemination and fibrinous serositis, rather than localization to the intestinal epithelium.[8]
2. Earlier onset of cell-associated viremia.[31]
3. Shorter incubation period, with earlier onset of clinical signs.[22]
4. Earlier onset of hematologic abnormalities, including thrombocytopenia and lymphopenia.[31]
5. More fulminating clinical signs with decreased survival times.[18, 22, 30 31]

Seronegative kittens failed to show clinical signs until seroconversion occurred.[33] Similarly, seronegative kittens passively immunized with feline serum containing high-titered antibodies reactive with FIPV developed a more fulminating clinical disease after FIPV challenge than did those pretreated with FIPV negative serum.[33]

The immunopathogenesis of FIP has been compared with dengue hemorrhagic fever (DHF) of man.[33] An arboviral infection mainly affecting children in tropical climates, DHF is transmitted by the mosquito *Aedes aegypti*. Affected individuals develop an abrupt onset of constitutional signs, followed in about 50 per cent of cases by hemorrhagic manifestations. Primary dengue infections apparently sensitize the person to a deleterious secondary antibody response upon reinfection with a heterotypic strain of virus.

Summary

The development of FIP may involve numerous predisposing factors, including age, genetic susceptibility, general physical condition, presence of concurrent diseases (such as FeLV), challenge dose and strain of FIPV, route of infection, previous sensitization with coronaviral antibody, macrophage function, and cell-mediated immunocompetence. It is not surprising, therefore, that FIP is a sporadic disease that appears unpredictably in the feline population.

Previously acquired or newly formed antibody does not appear to be protective; it accelerates the pathogenesis of the disease. The type of immune response formed by the cat may determine resistance or susceptibility and the type of clinical disease manifested. Cell-mediated immunity may be important in resistance to FIPV infection.[20] The lesions of noneffusive FIP suggest that incomplete control of infection is occurring through a partial cell-mediated immune response.[21] Paradoxically, there is preliminary evidence that noneffusive FIP may occur more frequently in cats with heterotypic FECV immunity.[23] Much has yet to be learned about the early pathogenesis of FIP, and it is likely that the sequence of events proposed in this article will change considerably in the future.

CLINICAL MANIFESTATIONS OF FIP

Cats at Risk

Both domestic and wild cats are susceptible to infection with FIPV. The reader is referred to the article titled "Infectious Diseases of Non-

domestic cats" for further discussion of these aspects of the disease. The disease occurs predominantly in young animals, although cats of all ages are susceptible. Peak incidence occurs between 6 months and 2 years of age. A decline in incidence is noted from 5 to 13 years of age, followed by an increased incidence in cats 14 to 15 years old.[20] Although male cats were considered at risk in earlier studies,[26] male and female cats are most likely affected to the same extent.[20]

FIP occurs more frequently in purebred cats, probably because these cats are often kept in catteries or multiple-cat households. Young susceptible cats in these environments may undergo prolonged exposure to a high concentration of coronaviruses and FeLV.[20] Several siblings in a litter, often the smaller and weaker kittens, may become infected.

Forms of FIP

Three forms of the disease have been recognized: (1) effusive FIP, characterized by fibrinous serositis and abdominal and/or thoracic pyogranulomatous effusions; (2) noneffusive FIP, characterized by marked pyogranulomatous lesions in parenchymatous organs, the central nervous system, and/or the eyes; and (3) combinations of these two.[5]

The qualitative and quantitative nature of the humoral and cell-mediated immune responses of the cat may determine the severity of the inflammatory response that develops. Changes in immune response may take place during development of disease, because it has been observed that noneffusive FIP may be preceded in some cats by transient effusive disease.[23]

Effusive FIP

Clinical Signs. Effusive FIP is the more fulminating form of the disease, with survival times being considerably shorter than for cats with noneffusive disease. In the early stages, cats are often presented with nonspecific signs, including chronic fluctuating antibiotic-resistant fever, anorexia, lethargy, and progressive weight loss. Mucous membrane pallor is often present, and, in severe cases, icterus may be noted due to hepatic involvement.[5] Fluctuating bouts of diarrhea and constipation are occasionally observed.

Progressive abdominal distension develops as a consequence of the accumulation of pyogranulomatous exudate in the peritoneal cavity. The volume of fluid varies, being greatest in chronic cases in which a liter or more may be present.[5] Abdominal palpation usually elicits no signs of pain. In some cats, the omentum may be palpated as a contracted fibrinous mass in the anteroventral abdomen.

In about 25 per cent of cats, pleural effusion may be present, causing decreased exercise tolerance, dyspnea (especially upon handling), and muffled heart and lung sounds. Pericardial effusion may also be present.[27] In intact male cats, scrotal enlargement may occur, resulting from a direct extension of the fibrinous serositis from the peritoneal cavity.[20] Ocular and central nervous system signs are infrequently seen in effusive FIP.[20]

The peritoneal or pleural fluid is pale yellow to golden clear or slightly opaque, sticky, and viscous. A stable foam often develops after shaking,

Figure 2. Multifocal fibrinous plaques on the intestinal serosa of a cat with effusive FIP. Mesenteric lymphadenopathy is also present. (Photograph courtesy of Dr. Geoffrey Saunders, Virginia Tech.)

probably reflecting the high protein content. Fibrin strands and flakes may be present, which settle with time. Fluid specimens may clot upon exposure to air.[20, 27] Cytologic smears are characteristic of a pyogranulomatous exudate (see Fig. 1). On stained smears, a pink granular background composed of protein aggregates may be mistaken for bacteria. The reader is referred to other sources for further details on fluid examination.[5, 20, 26, 27]

Pathologic Lesions. The visceral and, to a lesser extent, parietal peritoneum is covered by a diffuse or multifocal plaque-like, white, necrotic, fibrinous exudate that is often most evident on the liver and spleen (Fig. 2).[10] In chronic cases, fibrinous adhesions may develop between abdominal viscera.[10] Mesenteric lymph nodes are often enlarged (see Fig. 2). The mesentery is often thickened and may have a watery, gelatinous consistency.[9] The omentum may appear as a contracted thickened mass of fibrinous adhesions in the anterior abdomen. In cases with thoracic involvement, a similar fibrinous exudate affects the pleura and pericardium.

The exudate on serosal surfaces is mainly composed of fibrin with some nuclear debris, necrobiotic neutrophils, histiocytes, lymphocytes, neocapillaries, and fibroblasts.[10] Mesothelial hyperplasia is also present.

Noneffusive FIP

Clinical Signs. Nonspecific signs of weight loss, antibiotic-resistant fever, and malaise may last for several weeks before organ-specific manifestations appear. The early diagnosis of noneffusive FIP is hindered by a lack of localizing signs. Clinical signs reflecting involvement of the peritoneal cavity, central nervous system, or eyes are most common.

Abdominal palpation may reveal significant mesenteric lymphadenopathy (Fig. 3*A*) and nodular irregularities (caused by surface-oriented pyogranulomas) on the surface of viscera, especially the kidneys (Fig. 3*B*). Pyogranulomatous pneumonia occurs infrequently, usually unaccompanied by signs of respiratory distress. Lesions consist of peribronchiolar mixed inflammatory-cell infiltrates[20] and appear radiographically as ill-defined, patchy, interstitial and peribronchiolar densities[27] (Fig. 3*C*).

Pathologic Lesions. Pyogranulomas, usually appearing as raised, white foci from 1 to 20 mm in diameter, characterize the lesions of noneffusive FIP. Lesions tend to be subcapsular and surface-oriented but extend into

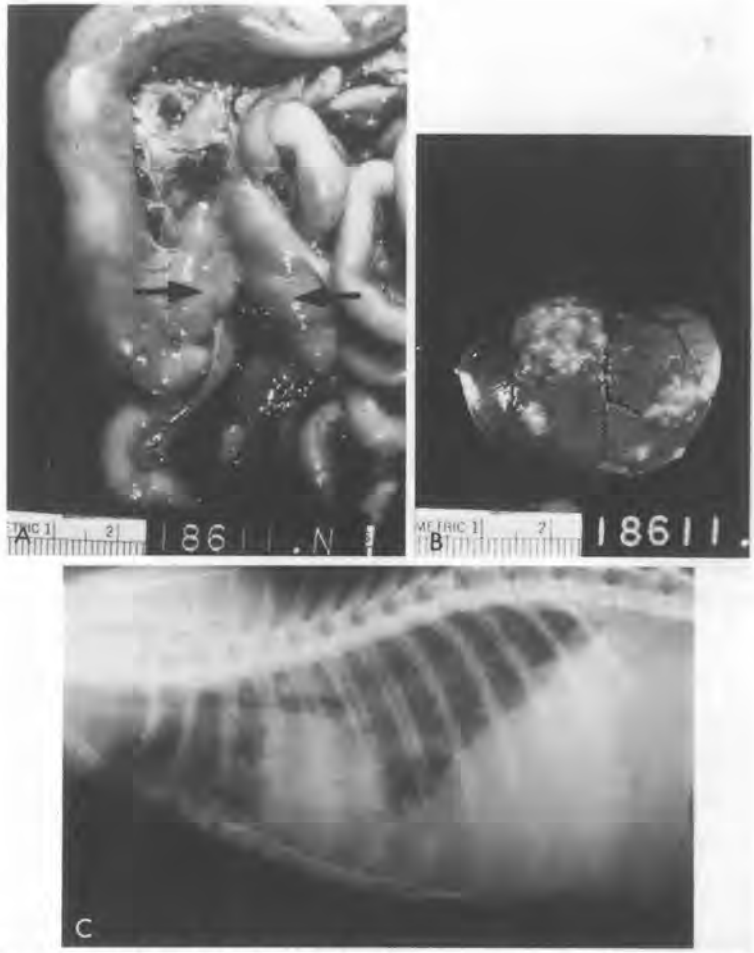

Figure 3. *A*, Enlarged ileocolic lymph nodes *(arrows)* in a cat with noneffusive FIP. *B*, Multiple, small, subcapsular pyogranulomas in the kidney of a cat with noneffusive FIP. *C*, Multiple, ill-defined, interstitial and peribronchiolar densities in the lungs of a cat with pyogranulomatous pneumonia that is due to noneffusive FIP.

the parenchyma of involved organs (see Fig. 3*B*). Renal pyogranulomas may be large enough to be confused with nodular lesions of renal lymphosarcoma. Smaller kidney lesions may have an arborescent pattern as a result of their association with large, subcapsular blood vessels.[9] Pyogranulomas are also found in mesenteric lymph nodes, liver, spleen, pancreas, omentum, and serosal membranes. Omental and serosal lesions are more focal, fibrinous, and organized, and less edematous than those occurring in effusive disease.[18]

Histopathologic examination of pyogranulomas reflects the immune-mediated basis of the disease and appears as a necrotizing vasculitis and perivasculitis. Variable coagulative necrosis may be present and associated

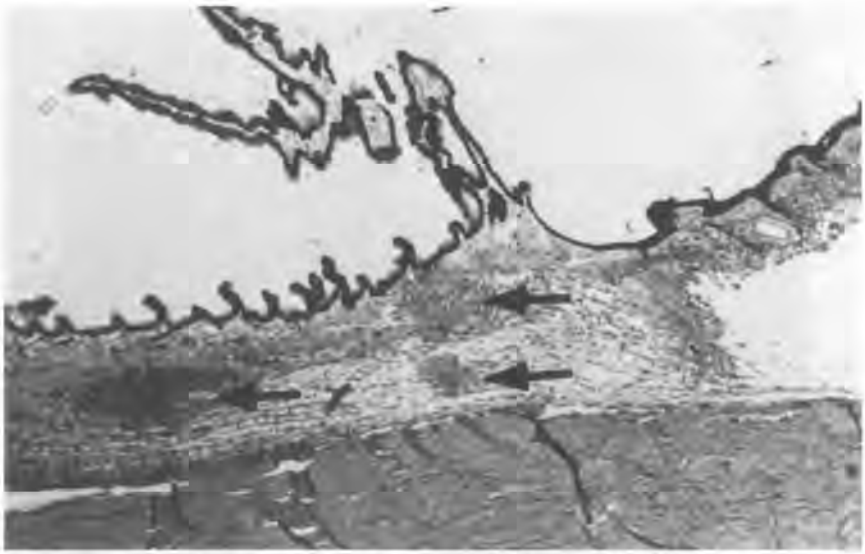

Figure 4. Multiple pyogranulomas *(arrows)* in the ciliary body of a cat with uveitis that is due to noneffusive FIP.

with intense perivascular infiltrations of neutrophils, and, to a lesser extent, macrophages, plasma cells, and lymphocytes.[16]

Ocular Manifestations of FIP

Ocular signs usually occur in association with other signs of noneffusive FIP but may be present without any signs of systemic illness.[20] Lesions develop as a result of a necrotizing and pyogranulomatous uveitis, which is localized around vascular structures (Fig. 4). Changes in the anterior chamber include corneal edema, aqueous flare, hypotony, iritis (Fig. 5*A*), hyphema, hypopyon (Fig. 5*A*), and keratic precipitates (Fig. 5*B*).[13, 15, 20]

On fundic examination, flame- or boat-shaped retinal hemorrhages may be evident. Engorgement of retinal veins and perivascular cuffing is often seen (Fig. 6). Choroidal inflammation may cause subretinal fluid exudation and secondary bullous or linear retinal detachments.[13] Histopathologic changes are found primarily in the iris, ciliary body, choroid, and retina.[13]

Neurologic Manifestations of FIP

The central nervous system manifestations of noneffusive FIP have recently been reviewed.[4, 20] Presenting signs are variable and include progressive incoordination, posterior paresis, nystagmus, convulsions, intention tremors, cranial and peripheral nerve paralysis, hyperesthesia, generalized ataxia, head tilt, behavioral changes, and urinary incontinence. Posterior paresis, convulsions, and nystagmus were the most frequent signs observed in one series.[14]

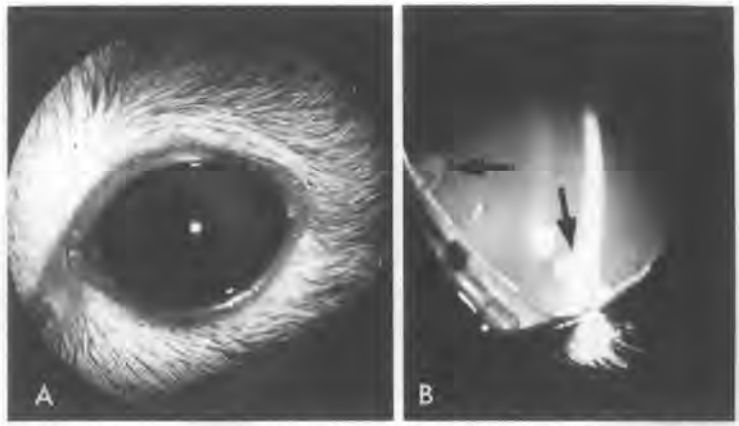

Figure 5. *A*, Hypopyon and iritis in a cat with noneffusive FIP. (Photograph courtesy of Dr. David Whitley, University of Florida.) *B*, Keratic precipitates *(arrows)* adherent to the ventral corneal endothelium of a cat with noneffusive FIP. (Photograph courtesy of Dr. R. A. Albert, Auburn University.)

Pathologic changes are typically multifocal or diffuse and surface-oriented, affecting primarily the choroid plexus, meninges (Fig. 7), and ependyma. These regions of the central nervous system may be prone to immune complex and/or cell-mediated injury.[4] Gelatinous masses of fibrinous exudate may obstruct the normal flow of cerebrospinal fluid, resulting in hydrocephalus. Histologically, lesions are characterized as a pyogranulomatous meningoencephalomyelitis. Lesions, as expected, are often oriented around small blood vessels, especially venules.[4] Many cats with noneffusive FIP that are not manifesting overt neurologic signs have histopathologic evidence of central nervous system involvement.[14]

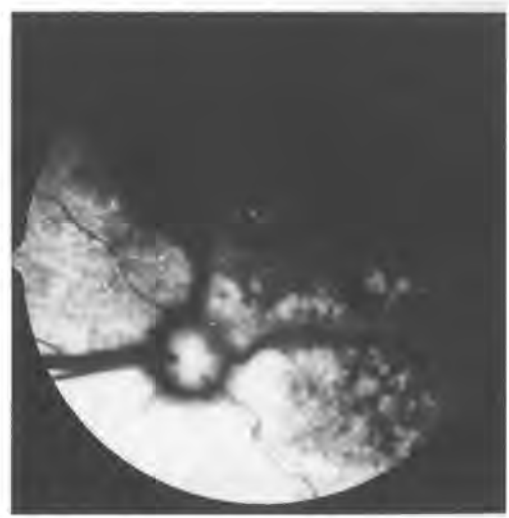

Figure 6. Retinal venous engorgement and perivascular cuffing *(arrows)* in a cat with noneffusive FIP. (Photograph courtesy of Dr. R. A. Albert, Auburn University.)

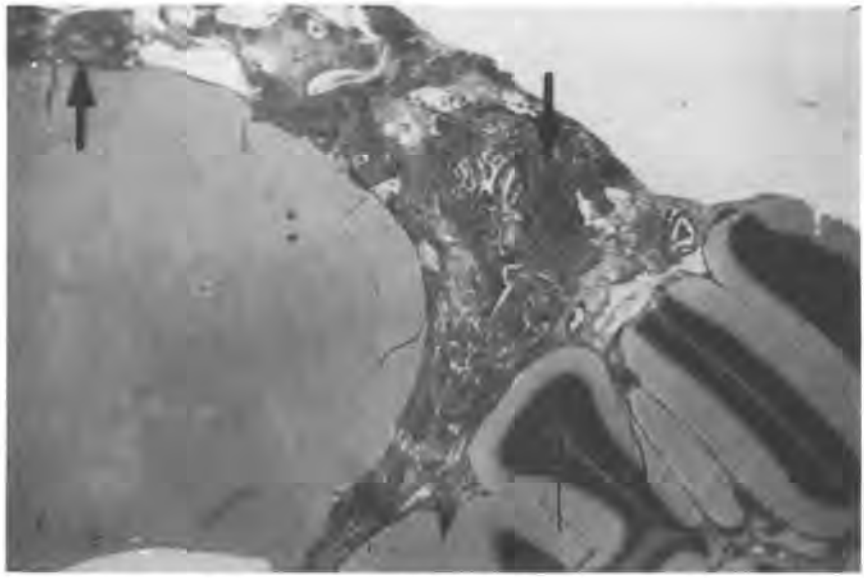

Figure 7. Pyogranulomatous meningitis in a cat with noneffusive FIP. Multiple pyogranulomas *(arrows)* are present within a mass of exudate overlying the cerebral cortex and cerebellum.

DIAGNOSIS, MANAGEMENT, AND PREVENTION OF FIP

Diagnosis

Accurate management of cats with suspected FIP requires careful correlation of physical findings, laboratory results, and coronaviral serology. It is beyond the scope of this article to review the laboratory diagnosis of FIP, and the reader is referred elsewhere for this information.[5, 20, 26]

Overreliance and misinterpretation of coronaviral antibody titers have caused FIP to become the most overdiagnosed feline disease. The article "Serodiagnostic Aids and Management Practice for Feline Retrovirus and Coronavirus Infections" deals specifically with the limitations of this diagnostic test.

Treatment

Therapeutic regimens for selected patients with FIP rely on the use of immunosuppressive agents to reduce the immune-mediated inflammatory response.[5, 20] Unfortunately, long-term remissions are rarely achieved, because the infection is not eliminated.

Preliminary clinical trials using new immunomodulating drugs* are

*MODU/FIP. Midwest Veterinary Pathology Laboratory, Inc., Harrison, Ohio.

presently underway, and initial anecdotal reports are variable. Although the exact mode of action is presently unclear, the potential benefits of such agents may originate from their stimulatory action on the cell-mediated immune system.

Prophylaxis

The antibody-mediated pathogenesis of FIP poses a special problem in the development of a safe and effective vaccine. Kittens vaccinated with an avirulent strain of FIPV were not protected from oronasal challenge with virulent virus. Paradoxically, vaccinated kittens were more readily infected than unvaccinated littermates.[21] Immunization with very small amounts of virulent FIPV induced protection in some cats and clinical disease in others negating its use as a consistently safe vaccine.[21] In the absence of a sensitizing humoral response, vaccines that stimulate cell-mediated immunity may be necessary.

SUMMARY

Mainly through studies inducing experimental infection of susceptible cats, significant advances have recently been made in our understanding of the pathogenesis of FIP. Much of this knowledge should not presently be directly extrapolated to field cases of FIP, because the route of infection and challenge dose and strain of virus may be significantly different. Advances in the prevention and treatment of FIP will depend greatly on clarification of the exact nature of the several coronaviruses affecting cats and the role of cell-mediated immunity in resistance to FIPV.

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