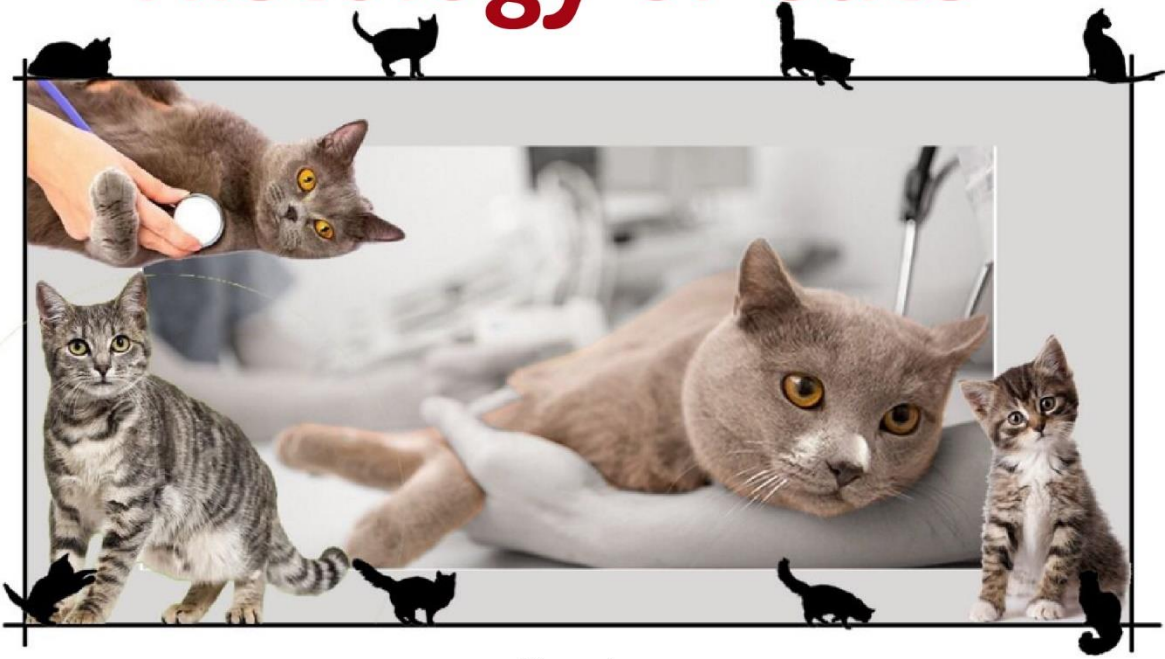
Challenging Diagnosis; Infectious Peritonitis and Histology of Cats



Yazarlar
Enes Turan SEVAL
Hatice YAREN KULOĞLU

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Challenging Diagnosis; Infectious Peritonitis and Histology of Cats

Yazar: Enes Turan SEVAL & Hatice YAREN KULOĞLU

Editör: Prof. Dr. Hikmet Yeter Çoğun

ISBN: 978-625-372-139-8

Page Layout: Gözde YÜCEL

1st Edition:

Publication Date: 25.12.2023

BIDGE Publications

Certificate No: 71374

www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com

Krc Bilişim Ticaret ve Organizasyon Ltd. Şti.
Güzeltepe Mahallesi Abidin Daver Sokak Sefer Apartmanı No: 7/9 Çankaya / Ankara


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Yayınları

PREFACE

The Coronaviruses (FCoV), which cause significant gastroenteritis in cats, are the main cause of Feline Infectious Peritonitis (FIP). While Feline Enteric Coronaviruses (FECV) usually cause a mild infection at the beginning, mutation of the virus leads to the development of FIP infections, which are much more contagious and fatal for cats. The majority of infected or uninfected cats are carriers, and when their immune systems are weakened, Feline Infectious Peritonitis (FIP) infection develops and the disease occurs. This infection is more common, especially in very old or very young cats with suppressed immune systems, in extreme stress situations, in crowded environments where cats live and shelter together and in cats with poor care and nutrition. The strong mutation ability of Coronavirus, the fact that cats act as carriers for a long time without showing any signs of infection, and the fact that cats spread the virus to the environment with their feces and secretions cause FIP disease to be widely seen among cats. Today, the lack of a definitive diagnosis of FIP infections, the difficulty of its treatment and the inability of existing vaccines to provide adequate protection make FIP one of the most important diseases for cats from past to present..

İÇİNDEKİLER

SYMBOLS and ABBREVIATIONS

A	Albumin
A/G	Albumin Globulin ratio
Ab	Antibody
ADA	Adenosine deaminase
Ag	Antigen
ALP	Alkaline phosphotase
ALT	Alanine aminotransferase
BUN	Blood urea nitrogen
CRP	C-reactive protein
ELISA	Enzyme-Linked Immunosorbent Assay
FCoV	Feline coronavirus
FECV	Feline enteric coronavirus
FIPV	Feline infectious peritonitis virus
FIP	Feline infectious peritonitis
FIV	Feline immunodeficiency virus
FLeV	Feline leukoma virus
G	Globulin
GRA	Granulocyte
HCT	Hematocrit

HGB	Hemoglobin
IFAT	Indirect fluorescent antibody test
KREA	Creatinine
LDH	Lactate dehydrogenase
LYM	Lymphocyte
MCV	Mean erythrocyte volume
MCH	Mean erythrocyte hemoglobin
MCHC	Mean erythrocyte hemoglobin concentration
MID	Monocyte
PCR-PZR	Polymerase chain reaction
PLT	Platelet
RBC	Total erythrocyte
SAA	Serum amyloid A
TB	Total bilirubin
TP	Total protein
WBC	Total leukocyte

1. INTRODUCTION

Feline Infectious Peritonitis disease was first discovered in 1960 and is a very important, fatal disease in cats. Two different serotypes have been identified for the virus, which is classified in the Alphacoronavirus genus within the Coronaviridae family. Apart from these classifications, Feline Coronavirus (FCoV) can be examined in 2 different biotypes, low pathogenic feline enteric coronavirus (FECV: low virulence FCoV) and high pathogenic FIP (Feline Infectious Peritonitis) virus (FIPV: high virulence FCoV). FIPV, which can be caused by disease-specific mutations in the feline enteric coronavirus (FECV), an important pathogen in cats all over the world, has been reported to be highly prevalent among crowded cat populations, such as shelter cats aged 9 weeks to 16 months (Pedersen, 2004; 2008; 2009). Although mainly seen in cats, coronaviruses can also occur in many mammals and poultry. While FCoV-infected cats can remain completely healthy, it is reported that one in 10 FCoV-infected cats develop FIP, often following the first infection. All cats carrying the FIP virus also carry FECV, but not all cats carrying FECV (Feline Enteric Coronavirus) will definitely develop FIP. After infection with FECV, clinical signs may last from 10-15 days to several months following illness. If there is no improvement, the disease progresses from subclinical to clinical form. While infections can occur in various regions, the subclinical form usually occurs in mesenteric lymph nodes (Pedersen and Black,

1983; Legendre and Bartges, 2009; Pedersen, 2009). In the clinical form of FIPV, complete recovery and disappearance of symptoms may, in rare cases, take months or even years. As a result of research, while coronaviruses can be seen in healthy animals and mammals, infected animals are very important in the spread of the virus. In infected and carrier animals, the virus can mutate and cause severe disease and even death in the infected animal. It can be easily transmitted, especially through free-ranging infected animals, if they are unvaccinated, and if infected cats carry the disease for a long time and spread the virus around with their feces and secretions. Since vaccinations against FIP are inadequate and its diagnosis and especially treatment are very difficult, the disease continues to be an important risk factor for cats today.

In the study, all aspects of Feline Infectious Peritonitis (FIP) disease and its histology were investigated and compiled.

1.1. ETIOLOGY

Coronaviruses in cats belong to the Coronaviridae family of the order Nidovirales. These viruses, together with the canine coronavirus (CCoV) and the infectious gastroenteritis virus of pigs (TEGV), are studied within the Alphacoronavirus-1 species of the Alphacoronavirus genus of the suborder Coronavirinae (Bas and Ok. 2020).

Coronaviruses have a very wide host range and are the leading cause of respiratory and/or intestinal infections in poultry and mammalian species. Coronaviruses, which are in the group of ribonucleic acid (RNA)-containing viruses, are thought to change and emerge through mutations and recombinations between large RNA genomes. The cases of severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012 caused by coronaviruses prove that this virus has the ability to mutate and the potential to pass between different hosts. Coronaviruses belong to the subfamily Coronavirinae of the family Coronaviridae in the order Nidovirales. Viruses such as infectious bronchitis virus in poultry, highly contagious gastroenteritis virus in pigs, coronavirus in dogs, feline coronavirus in cats, myocarditis agent in rabbits, sialodacriadenitis virus in rats and hepatitis virus in mice are among the main agents within the subfamily Coronavirinae. The genus Coronavirus, which is in the subfamily Coronavirusinae, is examined in three groups as alpha-beta-gamma coronaviruses. Alpha coronaviruses include coronaviruses of pigs, bats, dogs, cats and humans. Feline coronavirus (FCoV) belongs to the Alpha Coronavirus genus and consists of 2 separate serotypes characterized by the genetic and serological features of the spike protein. Serotype I FCoVs (FCoV I) are quite common and are responsible for 80% of FIP infection. Serotype II FCoVs (FCoV II) have been studied in more detail because they reproduce more easily in vitro, but this

serotype is less common. FCoV has two serotypes in nature: FECV and Feline infectious peritonitis virus (FIPV). FECV infection may cause asymptomatic or only mild gastrointestinal clinical symptoms. FIP virus can cause fatal symptoms such as fever, anorexia, diarrhea and weight loss. FCoV is divided into 2 different morphologies, type 1 and type 2. FCOV Serotypes 1 and 2 may differ in prevalence in different geographical locations, but there are no significant differences in their pathogenic potential. Type 2 FCoV infection spreads less than type 1 FCoV infection. While type 1 FCoV infection has a prevalence of 80%-95% in Europe and the United States, in a study conducted in China between November 2015 and January 2018 to analyze the genetic evolution of partial S genes and identified FCoV strains, type 1 FCoV was detected in 95% and type 2 FCoV in 5%. Many researchers claim that FIPV occurs as a result of FECV mutation. In these studies, it was reported that the probability of mutation was approximately 5% and consisted mostly of young or older cats. Factors affecting mutations include the animal's race, age, immunity, the presence of immunosuppressive diseases such as feline immunodeficiency virus (FIV) and feline leukoma virus (FLeV), the environment in which it lives, the enteric Coronavirus strain in its environment, surgical interventions and stress factors such as pregnancy (Kahraman, 2019).

1.2. EPIDEMIOLOGY

FIPV is transmitted to healthy animals through feces, urine and saliva of infected cats. FIPV virus is taken into the body via the oro-nasal route. There are also opinions that the mutant virus in FIP infection spreads among cats in different ways. Studies indicated that cats infected with FIP virus can spread both FIP virus and FECV, and that the FIP virus, which causes infection in susceptible cats, creates a predisposition for the development of the infection. In addition, it was revealed that the FIP virus do not cause infection in healthy cats and therefore, contrary to the opinion that "FIP virus cannot be transmitted from cat to cat", it was shown that FIP virus can also cause infection in susceptible animals. The disease has been reported to be seen not only in domestic cats but also in lions, cheetahs, mountain lions, leopards and jaguars. The incidence of FIP is approximately 1/5000 in cats. FIP is more common especially in cats younger than 24 months and older than 10 years. This infection has been reported to be more common in younger cats than in older cats, and in male cats than in female cats. Being housed in crowded or mass shelters, the presence of stray animals and carrier cats are important risk factors. Poor care and nutritional conditions, stress, parasitic infestations and the infections such as FIV and FLeV increase the likelihood of disease (Kahraman, 2019).

As a result of studies conducted in many other countries, it was stated that 30% of house cats and 90% of stray cats carry Coronavirus, and that the possibility of developing FIP in these cats always exists, depending on many factors. Studies conducted in Turkey found that the prevalence of FCoV infection varies between 16% and 70%. In addition, studies revealed that FIP was caused by both FCoV type I and type II in cats, and even both types of FCoV were isolated in some of the FIP-positive cats (Kahraman, 2019).

1.3. PATHOGENESIS

Although the pathogenesis of coronaviruses in cats is not yet certain, new information is being obtained every day. FCoVs need to attach to the host cell membrane in order to replicate. Binding requires specific binding sites on the S protein and surface receptor compatibility. Many Alphacoronaviruses are known to use aminopeptidase-N (APNCD13) as a cellular receptor. In vitro, FCoV S protein has also been found to use APN (especially the feline form -fAPN) as a receptor to enter the cell, similar to other Alpha-coronaviruses. APNs are cell surface glycoproteins (approximately 150 kDa) and cell surface metalloproteinases expressed by fibroblasts, renal neurons, respiratory and digestive tract epithelia, as well as granulocyte-monocyte stem cells. The first interaction between the virus and the cell is achieved by binding of the viral S protein to the receptor on the cell membrane. These interactions are

key in determining viral tropism and host diversity. Three factors stand out in the occurrence of FIP disease caused by this virus. These include systemic infection with mutated virulent FCoV (FIPV), efficient FIPV replication in monocytes/macrophages, and activation of FIPV-infected monocytes. Although not certain, mutation of FECVs to FIPV occurs during viral replication in monocyte/macrophage cells. Especially in cats with FIV, the 10-100 times higher replication cycle of FCoVs in macrophages supports the claims that it increases the risk of spontaneous mutation. Other factors that are effective in clinical disease are the route the agent enters the body, its amount, age, various stress factors, immunosuppressive disease affecting the immune system, and genetic susceptibility. Mutations in the S gene, either alone or in combination with other genes, are thought to contribute to FIPV-FECV biotype transformation. Mutations were identified in the S gene of the majority of FIPVs at 2 points that can be distinguished from FECVs. While 95% of FIPVs have one or two mutations, none of the FECVs have such a mutation. Therefore, it is suggested that the mutations identified are strongly associated with the pathogenesis of FIP . It is reported that deletions in the 7b gene (chromosome abnormality) may play an important role in the development of FIP. There are many opinions as to what makes FIPVs more virulent than FECVs. The main reason behind the higher virulence of FIPV is that it is not confined or fixed in one

tissue (FECV biotype in enteric epithelial cells), but systemically distributes and infects all cells of the organism (cellular tropism or affinity) with its strong tropism (affinity) towards macrophages and monocytes. This is the most important difference in the pathogenesis of FECV and FIPV. In cats, clinical disease is seen when the virus acquires the ability to replicate in monocytes/macrophages, which are the main elements for virulence. Transporting macrophages to target organs, the virus localizes in the reticuloendothelial system and perivascular areas of many organs. Viral RNA is also found in liver Kupffer cells (Kupffer-Browicz cells are specialized macrophages in the liver that form a part of the reticuloendothelial system). Viral RNA is found in different organs or tissues of cats persistently infected with coronaviruses, such as the gastrointestinal tract and blood. However, experimental studies have shown that in persistent infections with FECV, the main site for viral replication is the lower gastrointestinal tract (terminal ileum, large intestine and rectum). The mutated virus can be found throughout the body, including the cecum, colon, intestinal lymph nodes, spleen, liver and central nervous system, after approximately 2 weeks. In some cats, FCoV infections have been reported to induce macrophage or monocyte proliferation in hemolymphatic tissues. The mechanism or mechanisms that suddenly trigger monocyte activation in infected cats are still unknown. Circulating activated monocytes express excessive amounts of cytokines such as tumor necrosis factor-α

(TNF- α), IL-1β and adhesion molecules (such as CD11b and CD18). Furthermore, increased expression of enzymes such as matrix metalloproteina-9 in activated monocytes contributes to endothelial dysfunction and subsequent extravasation of monocytes (spreading out of the vessel and into surrounding tissues). It then facilitates the interaction of extravasated monocytes with activated endothelial cells in small and medium-sized vessels (veins). Moreover, vascular endothelial growth factors are produced in FIPV-infected monocytes and macrophages. Thus, vascular permeability increases and effusions may occur in body cavities. Although leukocytes are not susceptible to FIPV infections, they are activated by as yet unknown mechanisms. This is likely to contribute to endothelial cell damage and the development of FIP lesions. It is reported that viral replication in monocytes is initially very slow in FIP infections, but replication increases abruptly after the development of specific antibodies and continue for at least two weeks. Immunopathological damages are quite important in FIPV-infected macrophages. These cells are the most effective inflammatory cells in FIP lesions. Inflammatory mediators activate proteolytic enzymes that cause tissue damage. Complement fixation causes endothelial cell retraction (reduction or shortening of the volume of an organ or tissue), thus leading to the release of vasoactive amines that increase vascular permeability and the participation of neutrophil leukocytes in the inflammatory infiltrate.

The retraction of capillary endothelial cells leads to exudation of plasma proteins, resulting in the formation of the characteristic protein-rich exudate. Immune-mediated vasculitis activates the coagulation system and disseminated intravascular coagulopathy (DIC) occurs. With the activation of the complement system, other inflammatory mediator cascades, such as the blood coagulation Cascade (a sequence of chemical reactions in which the products of one reaction are burned in future reactions) can be activated. Cats without any clinical or pathological findings related to FIP can maintain viremia in their monocytes for 3 to 12 months. This indicates that the development of FIP is not only due to systemic spread, but is only one of the pathogenic events responsible for FIP. Genetic factors of the host are important for the susceptibility of monocytes to FCoV infection. The main reason for the low incidence of FIP in Siamese cats is thought to be related to the genetic predisposition to Niemann-Pick disease type C (NPC). In this genetic disease, cholesterol and other lipids cannot be transported into cells. In this rare genetic disease, large amounts of cholesterol accumulate in many organs such as the spleen, liver and brain. In an in vivo study conducted in areas endemic with FCoV, it was determined that a small percentage of cats remained seronegative or had a low antibody titer over a 5-year period (Bas and Ok, 2020).

The virus is transmitted between cats by the feco-oral route. The virus can reach the tonsils and small intestines within 24 hours following oral ingestion of particles and infect the secum, colon, mesenteric lymph nodes and liver within 14 days. It has been reported that virus spread through feces continues for periods ranging from 2 days to 10 months. The use of shared sand, food and water bowls is of great importance in the transmission of coronaviruses. Cats with enteric coronavirus infection may appear completely healthy, but in some of these cats, the coronavirus mutates into the form that causes FIP. While effusive FIP symptoms occur in these cats that do not develop an immune response, some develop a partial response and develop non-effusive FIP symptoms. Some cats do not develop the disease until reasons such as old age, other infections, stress, etc. suppress the immune system. Some cats are temporarily infected with the infection, while others remain carriers throughout their lives despite their healthy appearance (Yalçın and Keser, 2016).

1.4. DIAGNOSTIC METHODS

The diagnosis of coronavirus infections still poses some challenges in human medicine and is being intensively researched. Significant problems were encountered in the diagnosis and treatment of SARS-CoV-2 (Covid-19), a coronavirus that was detected in humans in late 2019 and reached pandemic level in 2020.

Therefore, intensive research was planned on the diagnosis, treatment methods and prevention of coronaviruses in humans. In cats, the diagnosis and treatment of FIP, which has been known for many years and is caused by coronaviruses, is still very difficult and controversial. This is due to the fact that the virulent coronavirus strain that causes FIP cannot be differentiated antigenically and genetically from other avirulent coronaviruses. Therefore, antemortem diagnosis of FIP remains challenging in clinical practice. In postmortem examination, immuno-histo-chemical diagnostic tests from biopsy samples are used as the standard diagnostic method of the disease. Recently, it has been suggested that sequence analysis differences between the S genes of FECV and FIPVs may be a diagnostic tool in the diagnosis of FIP. First of all, the diagnosis of clinical FIP cases is based on the cat's age, origin, physical examination and clinical findings. In environments with high cat populations, the presence of a persistent and fluctuating fever that does not respond to antibiotic treatment in cats aged 4-36 months is an immediate suspicion for FIP. These symptoms are known to be seen in some infectious diseases other than FIP. However, anamnesis and specific FIP symptoms may narrow the possible options in the diagnosis of the disease. In the clinical examination of patients, the presence of effusion findings along with abdominal tension, dyspnea due to pleural effusion, jaundice, hyperbilirubinuria, mass formations in the kidneys or mesenteric

lymph nodes, uveitis, and neurological findings related to the brain or spinal cord suggest FIP. At this point, a diagnosis of possible FIP can be made. An antemortem definitive diagnosis of FIP disease can be determined by direct immunofluorescence (DIF) testing in effusion fluid with a sensitivity of 100% and specificity of 71.4%. However, the probable diagnosis of the non-effusive form of the disease is more difficult as the clinical picture is not obvious. In cases with FIP, common laboratory abnormalities include chronic non-regenerative anemia, leukocytosis with an absolute increase in neutrophils and an absolute decrease in lymphocytes, high protein concentration with high serum globulin and low albumin concentration, and low A:G ratio. Although lymphopenia was found in 55-78% of cases with FIP, lymphopenia was found in only 49% of the cases, left-shifted neutrophilia in 39-57%, and mild-to-moderate normocytic normochromic anemia in 37-54%. There is a relationship between FIP and microcytosis. Hyperglobulinemia is detected in 88.9% of cases with FIP, and hypoalbunemia or low serum albumin concentration is usually detected in 64.5%. In cases of FIP, an A:G cut-off value greater than 0.5-0.8 may rule out FIP. However, it should be interpreted with caution and makes sense in combination with other diagnostic test results rather than examining A:G ratio alone. Hyperbilirubinemia is seen in 21-64% of FIP cases, particularly in the effusive form. Hyperbilirubinemia and hyperbilirubinuria may occur, usually without significant increase of

alanine aminotransferase (ALT), alkaline phosphatase (ALP) or γ-glutamintransferase (GGT) enzyme activities. Therefore, the presence of hyperbilirubinemia without severe anemia and high hepatic enzyme activities increases the suspicion of FIP. In cats with FIP, acute phase proteins change. In the diagnosis of FIP, an increase in the level of alpha-1 acid glycoprotein (AGP), which is an acute phase protein, although nonspecific, is important (mostly >1.5 mg/mL). In the early phase of FIP in cats, an imbalance in some cytokines (increase in TNF-α level and decrease in interferon-γ level) is noteworthy. In this disease, activation of macrophages induces the release of TNF-α. Thus, CD+4 and CD+8 T-lymphocytes undergo apoptosis and the level of aminopeptidase N (APN), the receptor of type II-FIPV, increases. In addition, ultrasonographic examination makes an important contribution to the detection of fluid and exudate accumulated in the chest and abdomen. The effusion fluid of cases with FIP is light to dark yellow in color, sticky and dense in consistency, and mostly contains fibrin fragments. (Baş and Ok, 2020). It is sterile if its density is between 1017-1048 and if there is no bacterial contamination. The effusion fluid kept in the refrigerator coagulates. The effusion fluid obtained from prospective patients is classified as exudate based on its high protein (>3.5 g/dL) and cell content (<5,000 nucleated cells/mL). Diagnostic methods such as serology (Baş and Ok, 2020) and PCR (Polymerized chain reaction), which are widely used in the diagnosis

of many diseases in human and veterinary medicine, cause some difficulties and contradictions in FCoV infections. The PCR test detects the nucleoprotein sequences of a specific virus. However, FCoVs also differ within themselves, and the biggest problem with FIPV is the lack of specific nucleoprotein sequences. In addition, some FCoVs invade through the intestines and cause a systemic infection. Therefore, the coronaviral protein sequence in blood serum does not confirm infection due to pathogenic coronaviruses. In addition, PCR, which is a sensitive test, may retain other RNAs in the laboratory environment and give false positive results. Therefore, laboratories where PCR is performed should have specialized equipment. Many studies have been conducted on the value of reverse transcriptase chain reaction (RT-PCR) in the diagnosis of cats with clinically suspected FIP. In these studies, the detection of FCoV RNA could not distinguish virulent FIP virus from avirulent FECV variants. Furthermore, conventional RT-PCR can also give positive results in healthy cats that do not show signs of FIP. RT-PCR in serum or plasma is not recommended for the definitive diagnosis of cats with suspected FIP due to the low viral load in blood. When various tissue samples (liver, mesenteric lymph nodes, bone marrow, kidney and/or spleen) of cats with possible FIP are examined by RT-PCR, FCoV RNA is detected in 88%. However, FCoV RNA is also detected in 33-85% of FECV-infected cats that appear clinically healthy. Therefore, it is stated that the detection of

FCoV RNA in tissues is not specific for FIP. In veterinary medicine, FIP is rarely diagnosed by RT-PZR in tissue samples. This test usually requires invasive tissue sampling via laparotomy or laparoscopy or can be performed post-mortem. Although RT-PCR in serum or plasma is not recommended for the diagnosis of cats with FIP, it is reported that the detection of FCoV RNA is reliable and specific, especially in the cerebrospinal fluid (CSF) of patients with neurologic or ocular signs. It is indicated that a positive FCoV result in the analysis of the effusion fluid of cats with effusive FIP by qRT-PCR (quantitative reverse transcriptase polymerase chain reaction) may be a useful diagnostic marker for the disease. Effusion fluids can be determined with high sensitivity by RT-PCR in the definitive diagnosis of cats with suspected FIP. In the antemortem diagnosis of cats with possible FIP (Baş and Ok, 2020), they recommend the detection of FCoV in macrophages with the DIF test of effusion fluid samples and suggest its use as a confirmation test since it has 100% specificity. In cats with effusive FIP, the detection of FCoV nucleic acid or specific antibodies alone in the effusion fluid is not guaranteed for the antemortem definitive diagnosis of the disease. Therefore, they recommend a combined serologic and molecular protocol (detection of antibodies serologically and RNA molecularly) in addition to clinical and hematological findings, that is, the combined application of these methods. The first analysis to detect anti-FCoV antibodies in cats was developed in 1975-1976 and

was the most misleading test. Contrary to expectations, this test was found to be insufficient to distinguish antibodies against FECV and FIPV. Therefore, high antibody titers in the blood are not considered a definitive indicator of FIP. Especially low and medium titers are of no value in the diagnosis of FIP. The disease-specific sensitivity and specificity of antibody detection in effusion fluids of patients histopathologically confirmed to have FIP are 85% and 84%, respectively. In 24% of patients, the antibody titer measured in the effusion fluid is lower than the serum antibody titer. In feline coronavirus infections, there is a negative correlation between serum FCoV antibody titer and FCoV viral load. Therefore, false-negative antibody results are likely in cats with high viral RNA. As a result, antibody titer in effusion fluid is reported to be more accurate than serum antibody titer in the diagnosis of FIP. The gold standard for the diagnosis of FIP is necropsy and histopathologic examination. In the effusive form of the disease, there are pyogranulomatous lesions in the form of small white plaques caused by the accumulation of large amounts of fibrin and inflammatory cells in one or more organs, and fluid accumulation in the thoracic and abdominal cavities. In the non-effusive (dry) form of the disease, no fluid accumulation is observed and lesions can be quite variable. In such cases, many variable lesions such as pyogranuloma in the renal cortex and thickening of the colonic wall can be detected. Granulomas or pyogranulomas can often be found in various organs,

especially in the lungs, liver, kidneys, intestines and central nervous system. Virus isolation is not clinically useful. The most effective method for detecting coronavirus RNAs in feces is RT-PCR. However, this test cannot distinguish between FIPV and FECV. However, in cats, negative coronavirus antibodies and fecal coronavirus RNA for 5-6 months are considered as the absence of disease (Baş and Ok, 2020).

1.5. CLINICAL FINDINGS

The clinical findings of FIP vary depending on the cat's immune system and whether the cat has been previously exposed to the infection. The incubation period may take weeks, months or even years, especially in dry FIP cases. Clinical FIP usually seen in cats aged 6 months to 5 years, especially those aged 6 to 24 months. However, it is also known that 8-week-old kittens die from FIP. In adult cats, FIP infection progresses in a chronic form that lasts for weeks, months or even years. Therefore, it is possible and realistic to attribute clinical symptoms to FIP in a cat that is older than 10 years old and has not been outside the house until that day. It should also be taken into consideration that the infection can be transmitted from the mother (Aytuğ, 2009).

In cats infected with coronavirus, it is not clear whether clinical findings will be present, or in what form they will appear. Cats exposed to the agent for the first time may be asymptomatic,

showing mild diarrhea or upper respiratory tract signs. Some infected cats may exhibit signs of mild vomiting and diarrhea that may last for weeks or months. Most cases in this situation may not require treatment. It was confirmed in the late 1990s that feline enteric coronaviruses (FECV) can cause persistent infections similar to asymptomatic natural infections. If the virus is detected in the feces of such cases, excretion of the virus in the feces can last for months or years. In cats, viral RNA can be detected in blood and feces shortly after coronavirus infection. Serum antibody titer increases rapidly and remains at high levels throughout the infection. Some infected animals show signs of recovery in the first weeks after clinical symptoms appear. However, persistent fever, loss of appetite and deterioration in body condition may be observed during the course of the process. The incubation period is unknown in natural infections, but the subclinical phase can last for months or even years in a latent form. In experimentally infected cats, the incubation period can last 2 days to 2 weeks for the wet form and weeks for the dry form (non-effusive). In an experimental study, most cats infected with the virus died within 3 to 5 days following infection, and a small number succumbed to the disease after several months of survival. Survival time in experimental infections were reported to vary significantly depending on the concentration and virulence of the given virus. The time it takes for non-fatal FCoV infections to

transform into FIP cannot be predicted, but clinical findings occur as a result of random mutation (Baş and Ok, 2020).

FIP has three clinical forms: effusive (wet), nonfusive (dry) and mixed forms. The effusive form of the disease is more common than the non-effusive form. However, cases of both are also common. In addition, the clinical forms mentioned can also transform into each other. In feline coronavirus-associated FIP, the distribution of lesions characteristic of FIP varies depending on the cellular composition and viral antigen expression level. The disease is characterized by fibrinous and granulomatous serositis, protein-rich effusion in body cavities, and granulomatous lesions. Clinical and pathological findings may occur as a direct result of organ failure and vasculitis caused by damage to blood vessels. Studies conducted in naturally infected cats have shown that vasculitis is a result of the interaction between monocytes and activated endothelial cells. On the other hand, pathological findings related to hypersensitivity reactions may also occur secondarily during the development of vasculitis due to monocyte activation. Subclinical disseminated intravascular coagulopathy (DIC) was detected in an experimentally infected cat. In FIPV-infected monocytes, vascular endothelial growth factor is released due to monocyte activation. Thus, vascular permeability is greatly increased and effusion formation is induced. The effusive (wet) and non-effusive (dry) forms of FIP are often

described as different syndromes. A severe inflammatory response results in disease-specific vasculitis and pyogranulomatous lesions. The effusive form is characterized by fibrinous peritonitis, pleuritis or pericarditis in the thorax, abdomen or pericardium. Most cats with FIP develop effusion and often exhibit abdominal tension or bloating (Figure 2). In these patients, the incidence of ascites characterized by abdominal tension is higher than cardiovascular, neoplasia, hepatic or renal diseases. At least 60% of cats with effusions are thought to have FIP. Ascites in cats with effusion is usually characterized by abdominal, thoracic, and/or pericardial fluid accumulation. On palpation of the abdomen, there is a fluid wave, and in less severe cases, fluid can be observed between the intestinal lobes. Some cats with effusion are depressed, while others are in a good condition. Sick cats with effusions can sometimes have a normal appetite and sometimes be anorectic. Weight loss, organ failure, and fever are seen in cats with severe effusion. Patients with thoracic effusions often have signs of dyspnea, tachypnea or respiratory distress and cyanotic mucosa. Pericardial effusion may also be seen in some patients with effusion. In such patients, muffled heart sounds are heard on auscultation. In this case, significant changes in the ECHO or EKG are noticeable. In cats with general effusion diagnosed with probable FIP, abdominal effusion was found in 62% of the cases, thoracic effusion in 17%, and effusion in both body cavities in 21%. In a similar study, thoracic effusion was

detected in 30% of cases with general effusion, and abdominal and thoracic effusion together in 30%. Therefore, in cats with effusion, the possible diagnosis of FIP is evaluated first. In the non-effusive or dry form of FIP, there is little or no effusion. These patients are generally characterized by granulomatous changes in their organs (Gökçe and Cengiz, 2019).

Clinical findings are usually unclear in cats with the non-effusive form. However, fever, weight loss, lethargy, loss of appetite and occasional jaundice are seen. In cases where the lungs are affected, dyspnea and radiographic damage to the lungs are observed. During abdominal examination of patients, enlargement of mesenteric lymph nodes, abnormal kidney morphology or nodular lesions in internal organs may be observed. In cases of FIP with central nervous system (CNS) involvement, the clinical picture varies depending on which tissue or organ is affected and its severity. Neurological findings may be observed in at least 10% of cases with FIP. Clinical findings related to the central nervous system may include upper neuron paresis, ataxia, nystagmus, behavioral changes and seizures, as well as cerebral or cerebromedullary lesions due to spinal cord involvement. In cats of all age groups, the most common cause of spinal cord disease is lymphoma or vertebral neoplasia. However, these findings can also be seen in cats with FIP under 2-2.5 years of age. Posterior paresis, incoordination, hyperesthesia,

seizures and paralysis of the brachial, trigeminal, facial and sciatic nerves were reported in patients with medulla spinalis involvement. In some cases, hydrocephalus was observed as a result of involvement of the plexus choroidus and ependymal cell layer. In addition, cerebellar-vestibular symptoms (nystagmus, head shaking and turning), behavioral changes (such as aggression and hiding) and convulsive disorders may also be observed. In a cat confirmed immunohistochemically to have meningoencephalomyelitis due to FIP, weight loss despite normal appetite and many chronic, progressive and painless neurological findings were determined. Extensive clinical and laboratory examination of these cats revealed nonregenerative anemia, ataxia and paraparesis (partial paralysis of 2 legs) after 2.5-3 months, tetraparesis (partial paralysis of 4 legs), tail paralysis, loss of body control and inability to control urine and feces within the next two months. At necropsy of the patient, the diagnosis of FIP was confirmed immuno-histo-chemically from the tissues. Specific and functional amino acid changes were determined by molecular analysis of the coronavirus spike protein in the central nervous system (CNS)-related tissues of this patient, such as the brain and spinal cord. In clinical cases of FIP, lesions in other organs are also accompanied by ocular lesions. However, in some cases, only ocular lesions may be present. In cases of FIP, the most common ocular clinical course is uveal region damage resulting in iritis, uveitis or chorioretinitis. Retinal hemorrhage and detachment

or panophthalmitis may also occur. The first symptom associated with FIP disease in the eyes is color change in the iris. In cases of FIP, keratinous precipitates formed in the caudal part of the cornea are characteristic, and microscopic accumulation of fibrin, macrophages and other inflammatory cells is observed here. The most common infectious causes of uveitis/chorioretinitis in cats include FIP and, less commonly, FeLV-associated lymphoma, trauma, toxoplasma, and lens-associated uveitis. Clinically, especially in the initial stage of the disease, in addition to all these special findings, persistent fever may be the only clinical finding (Baş and Ok, 2020).

A diffuse vasculitis is observed in the wet form. In this form, as vascular permeability is impaired, protein-rich fluid accumulates in the abdominal and thoracic cavities. Abdominal tension, hydrops ascites and painless fluctuation in the abdominal cavity are felt during palpation. The fluid is golden yellow, clear and mucinous in character. The pressure of the fluid on the diaphragm may cause difficulty breathing, wheezing and scrotal enlargement in male cats. Death in kittens is caused by pleuritis, hepatitis and bronchitis. Synovitis and lameness may occur as a result of antigen-antibody complex accumulation in the joints (Kahraman, 2019).

In Cats with Infectious Peritonitis, the dry form is generally seen in cats aged 10 years and above and in this form, granulomatous

or pyogranulomatous lesions develop in various organs. Since the lesions progress from the pleural and peritoneal tissues towards the parenchyma, this form is also known as the parenchymatous form. Inflammatory cells accumulating in the organs cause local tissue necrosis and dysfunction, and this area turns into a pyogranulomatous lesion over time. Macroscopically, gray-white nodules are seen in the parenchymal tissue of the organ. In this form, the kidneys and mesenteric lymph nodes are more affected, while the liver and other lymph nodes are less affected. Ulcerative colitis, typical of the dry form, develops as a result of the involvement of the rectum and colon. Feces may be covered with mucus and blood. Heart attack may occur as a result of parenchymatous lesions of the pleura and liver progressing and affecting the pericardium (Kahraman, 2019).

Central nervous system (CNS) signs have been identified in 10% of cats with FIP and are most common in cats under 2 years of age. In cases where the spinal cord is affected, numbness, incoordination, hypersensitivity, ataxia and tremors may occur in the forelimbs. Hydrocephalus may develop due to involvement of the choroid and ependyma layers of the brain. As a result of cerebellar-vestibular lesions, head tilting, nystagmus, and turning around itself are observed. In the dry form, color change and granulomatous lesions in the iris and shape change in the pupil may be observed

after uveitis and chorioretinitis. In addition, anhidrosis, myosis, enophthalmus, ptosis, heteroktomia and horner's syndrome are also among the important findings in FIP. CNS lesions are frequently observed in the leptomeninges, ventricles, choroid plexus, and sometimes neuroparenchyma (Kahraman, 2019).

Clinical symptoms vary depending on the form of the lesion and organ distribution, and in cases with central nervous system lesions, neurological symptoms such as depression, ataxia and seizures are observed in 85% of cases. In cases of FIP in cats, fever and weight loss are common findings in both forms, and icterus and anemia may also be observed in some cats under 2 years of age (Kahraman, 2019).

1.6. HISTOLOGICAL FINDINGS

Histological examination was performed on 93 tissue and blood samples taken from cats with FIP, and 83 of them were obtained from cats without FIP. Significant macroscopic changes were observed in samples taken from cats with FIP. Overall, 55/93 tissues (59.1%) of cats with FIP were reported to exhibit histological features consistent with the disease. Different types of lesions consistent with FIP can often coexist in the same animal or even in the same organ. Most cats in the FIP group (11/14, 78.6%) actually showed lesions consistent with FIP in more than one patient. Although fibrinous serositis is generally always present, mesenteric

lymph nodes are commonly affected by Fibrinous serositis especially in the spleen, liver and lungs, while Fibrinous serositis is detected with granulomatous lesions and often vasculitis. Lymphoplasmacytic infiltrates or vasculitis are observed along with granulomatous/pyogranulomatous lesions. Histological lesions compatible with FIP were found in cats with neurological signs. With severe or chronic diagnosis, lymphoplasmacytic meningoencephalitis and ependymitis are seen only in the central nervous system (CNS). Histological sections examined (38/93 tissues, 40.9%) did not show relevant lesions or lesions compatible with FIP. The tissues showing the most common typical histologic lesions in the FIP group were lung, kidney and mesenteric lymph nodes. Then, the liver, spleen, and small and large intestines were among the organs less affected by FIP-related lesions. In the histological examination of the non-FIP group, lesions potentially compatible with FIP were found in 77/83 samples (92.7%). In 6/83 tissues (7.2%) collected from 3/12 cats (25.0%), lesions compatible with FIP were observed in the kidney, which was the most common, followed by lymph nodes, spleen and liver. No lesions compatible with FIP were detected in the small and large intestines. In a few cases, they were compatible with the histological results but were not highly significant for FIP and can be classified as negative or positive based on findings in other tissues. Specifically, 5/93 tissues from cats with FIP showed lesions suspicious for FIP, and three were

categorized as negative (small intestine). Two of them were determined positive (lymph node and kidney) in the large intestine. The histology was not definitive in only 1/83 samples from cats without FIP, and the sample was categorized as positive based on the cat's lung findings in other tissues (Stranieri et al, 2020).

1.7. LABORATORY FINDINGS

While there is usually an increase in total leukocyte counts in both dry (Non-effusive) and wet (Effusive) forms, decreases can sometimes be detected. While neutrophil counts increase significantly, lymphocyte counts decrease. The increase in neutrophil count is known to be the result of a stress leukogram, which is frequently seen in cats. In addition, a large proportion of cats with FIP develop moderate anemia, and it is stated that anemia is a common condition in chronic infections in cats (Gökçe and Cengiz, 2019).

An increase in total protein was also detected in cats with FIP due to an increase in gamma glubulin, and hyperglobulinemia was found in 50% of cats with wet form FIP and in 70% of cats with dry form FIP. The albumin level was lower than normal in most cases with FIP, and the Albumin Globulin ratio (A/G) was generally below 0.8. There were also increases in Hyperbilirubinemia, azotemia, creatinine, ALT and ALP levels in cats with FIP. In addition, in studies conducted in cats with FIP, significant increases were

determined in the levels of alpha-1-acid glycoprotein (α1-AGP) and serum amyloid A (SAA), which are acute phase proteins. Protein and leukocyte count increased in the cerebrospinal fluid (CSF). In peritoneal fluid analysis, the fluid was light-dark yellow, sticky and dense in consistency. It mostly contained fibrin fragments and its density was between 1017-1047 (Gökçe and Cengiz, 2019).

In the hematologic analyses performed in cats with FIP, total leukocyte (WBC) ($p<0.001$), neutrophil ($p<0.001$) and monocyte ($p<0.001$) counts were found to be significantly higher than the control group, while lymphocyte ($p<0.01$) and erythrocyte (RBC) ($p<0.001$) counts of the FIP group were found to be significantly lower than the control group. It was determined that cats with FIP had granulocyte-derived leukocytosis and moderate anemia. (Gökçe and Cengiz, 2019).

Biochemical analysis of cats with FIP and healthy cats revealed that there were significant increases in the ALT ($p<0.01$), LDH ($p<0.01$), ALP ($p<0.01$), TP ($p<0.01$) and globulin ($p<0.05$) values of cats with FIP compared to the control group. On the other hand, there were significant decreases in the albumin ($p<0.01$) and albumin/globulin ($p<0.01$) ratios of cats with FIP compared to the control group. According to the cut-off values determined separately for each parameter, some animals showed an increase or decrease in

the analyzed values, while the values of some animals were found to be within normal limits. (Gökçe and Cengiz, 2019).

In the comparison of the biochemical parameters of the cats with dry form and wet form FIP, only the total protein and globulin values of the cats with dry form were significantly higher than those with wet form ($p<0.05$), while no statistically significant differences were found between the two groups in the other parameters analyzed.

As a result of serum ADA-1, CRP and albumin analysis of cats with FIP and control group, it was determined that serum ADA-1 ($p<0,001$) and CRP ($p<0,001$) levels of cats with FIP were significantly higher than those of the control group, while albumin ($p<0,01$) concentration was significantly lower. Increases in serum ADA-1 and CRP levels of cats with FIP showed a positive correlation, while decreases in albumin levels showed a negative correlation (Gökçe and Cengiz, 2019).

The increases or decreases were determined for each parameter according to the calculated cut-off points. Accordingly, 70% (14/20) of the cats with FIP had an increase in ADA-1 level, 6 of these increases were in dry form (6/10, 60%) and 8 of these increases were in wet form (8/10, 80%). When serum CRP levels of cats with FIP were taken into consideration, increases in CRP levels were determined in 13 cats (65%), 5 (5/10, 50%) of these increases were in the cats with dry form and 8 (8/10, 80%) of these increases

were in the cats with wet form. When the increases in ADA-1 and CRP levels were examined, it was seen that there were increases in more cats with wet form (Gökçe and Cengiz, 2019).

In the study, ADA-1 levels of cats with wet form ($p<0.05$) were significantly higher than those with dry form. Although CRP levels of cats in the wet form were higher than those in cats in the dry form, no statistically significant increases were found between these two groups (Gökçe and Cengiz, 2019).

As a result of serum and peritoneal effusion ADA-1 and CRP analyses performed in 10 cats in the wet form, it was determined that both parameters were at high levels in both serum and peritoneal effusions, and the increase in ADA-1 levels was parallel to the increase in CRP levels (Gökçe and Cengiz, 2019).

While the BUN, TP, A, G values of cats with dry form were found to be higher than the values of cats with wet form, the A/G ratio was determined to be lower in cats with dry form FIP compared to the cats with wet form (Gökçe and Cengiz, 2019).

Increases in serum BUN and creatinine levels are used to determine renal failure, and serum BUN levels increase in cases of increased protein degradation. Creatinine, on the other hand, increases in serum when glomerular filtration in the kidneys is impaired. In the current study, increases in BUN levels were

determined in some animals, probably as a result of protein degradation due to inflammation. ALT is concentrated in liver cells and is also found in lower amounts in the heart, muscle, kidney and pancreas. An increase in its level in the blood indicates liver parenchymal damage or bile duct obstruction. LDH is found in high amounts in the liver, heart, kidneys, skeletal muscle and erythrocytes. Its blood level increases as a result of liver damage, muscle necrosis and destruction of erythrocytes. The enzyme ALP is concentrated in liver, intestine, kidney and bone cells. Its level in the blood increases in liver bile duct inflammation and bile stagnation, intestinal and kidney damage, bone degradation and increased bone activity. Bilirubin levels in the blood are higher in kittens than in adult animals due to high bone activity. Increases in total bilirubin levels with increases in liver enzymes without hemolysis are reported to indicate that liver function is affected in FIP. It is also reported that the occurrence of icterus along with hyperbilirubinemia indicates liver necrosis. In the present study, serum ALT ($p<0.01$), LDH ($p<0.01$) and ALP ($p<0.01$) levels of cats with FIP were significantly higher than healthy animals. In addition, TB levels were increased in some of the cats with FIP (65%). It was determined that increases in liver enzymes in cats with FIP varied depending on the severity of infection and the organ it affected. In this study, increases in liver enzymes and TB levels were detected in some cats with FIP, suggesting that the liver may not be affected in all cats with

FIP. Blood negative levels decrease in liver failure, long-term fasting, and in cases such as enteropathy, nephropathy, nephritis and nephrotic syndrome that cause excessive protein loss. Globulin levels generally increase in chronic diseases. In studies conducted in cats with FIP, it was determined that total protein and globulin levels increased while albumin levels decreased. It is suggested that the cause of hypoalbumin in cats with FIP is the loss from the kidneys and protein-rich fluid leaking into body cavities. In the present study, similar to previous studies, it was argued that if the total protein (p0.8) of cats with FIP was 0.8, these cats were most likely not to have FIP; however if A/G A/G<0.4, these cats were most likely to have FIP. Therefore, the A/G ratios obtained in the study also support that cats may have FIP. Total protein and negative levels were found to be higher in cats with dry form FIP compared to cats with wet form FIP, indicating that the power of the liver to synthesize negatively was not affected. However, as previously reported, protein-rich effusions and renal failure may have played a role in the development of hypoalbuminemia in some cats. However, in this study, the level of negative was low both in cats with effusions in wet form and in cats without effusions in dry form. In addition, when the creatinine and BUN levels of cats with FIP were taken into consideration, it was revealed that their renal functions were not seriously affected. Therefore, it is thought that the causes of hypoalbumin may include the loss of protein-rich effusions due to

vasculitis, the loss from the kidneys as a result of impaired glomerular filtration and the negative effect of the liver's ability to synthesize negatively (Kahraman, 2019).

In biochemical studies conducted in cats with FIP, increases were determined in total bilirubin, BUN, ALT, ALP, total protein, and globulin levels, while decreases were determined in albumin level and A/G ratios. It was suggested that the increase in BUN level may be due to glomerular dysfunction and the increase in liver enzymes may be due to inflammation. The increase in total protein level was attributed to the increase in globulin synthesis, while hypoalbuminemia was attributed to the leakage of protein-rich fluid in the vessels due to vasculitis and impaired reabsorption from the kidneys. Significant increases were detected in ALT ($p<0.01$), LDH ($p<0.01$), ALP ($p<0.05$), TB ($p<0.01$), TP ($p<0.05$) and G levels in cats with FIP, while significant decreases were determined in A ($p<0.05$) and A/G ($p<0.001$) ratios compared to healthy cats. It was seen that both the kidneys and liver in cats with FIP were negatively affected by the infection. BUN, TP and globulin levels were found to be higher in dry form compared to wet form, while A/G ratios were found to be lower in dry form. It was revealed that the kidneys were more affected in dry form FIP cases, more globulin was synthesized in these cats, and A/G ratios decreased more due to the increase in globulin. In addition, it was determined that albumin and

TP levels were lower in cats with wet form than in cats with dry form FIP (Gökçe and Cengiz, 2019).

1.8. NECROPSY

Necropsy findings should be evaluated by matching them with clinical findings. Inflammatory lesions, pyelogranulomatous changes, effusion and fibrin accumulation are present in the peritoneal and pleural organs. In the wet form, there is an accumulation of sterile, protein-rich fluid in the abdominal and thoracic cavities. No effusion is observed in the dry form. Granulomatous and pyogranulomatous lesions are detected especially in the lung, liver and kidney. These lesions are also found in the eye (Gökçe and Cengiz, 2019).

As a result of necropsy performed on deceased cats, abundant Rivalta test-positive protein-rich fluid was determined in the abdominal and thoracic cavities of cats with wet form FIP. In the dry form, widespread granulomatous formations were detected in the liver, lung, pleura, peritoneum and intestines (Gökçe and Cengiz, 2019).

1.9. TREATMENT – I

There is no effective treatment or prevention method for FIP. The main aim of treatment is to alleviate the inflammatory response caused by the disease with supportive treatment. Thoracocentesis

and abdominalsynthesis are recommended for cats with excessive fluid accumulation in the thorax and abdomen, and after these procedures, intra-abdominal or intrathoracic dexamethasone administration at a dose of 1 mg/kg once a day until the fluid accumulation disappears is beneficial. It is recommended to give oxygen at a rate of 100ml/kg/min to cats with respiratory difficulties. Since the immune system is suppressed, oral ampicillin at a dose of 10-20mg/kg can be given at 8-hour intervals to prevent bacterial infections that may develop. Since the formation of antigen-antibody complex is thought to be among the causes of vasculitis that develops in FIP in cats, it is suggested that immunosuppressive drugs be administered to these animals. For this purpose, prednisolone at a dose of 2 mg/kg is administered orally once a day, cyclophosphamide at a dose of 2.5 mg/kg is administered orally 4 days a week, and chlorambucil 20 mg (kg/m2 orally) is administered twice a day for 3 weeks. Ribavarin has been found useful as an antiviral but is not recommended due to its high toxicity (Addie et al., 2009; Carlson and Macintire, 2006; Pedersen, 2014). Recently, successful results have been obtained with a nucleoside analog GS-441524 (Murphy et al., 2018). In addition, studies suggest that human interferon alfa should be administered as an immunomodulator at a high dose of 104-106 IU/kg subcutaneously or at a low dose of 1-50 IU/kg orally once a day. However, especially recombinant feline interferon omega administrations were found to

be beneficial, and good results were obtained by initially administering 1 IU/kg subcutaneously every other day and then once a week in combination with dexemetazone or prednisolone, which was mostly aimed at prolonging the lifespan of cats (Addie et al. ., 2009; Carlson and Macintire, 2006). In a treatment study conducted in a cat with FIP, pentoxifylline (10-15mg/kg, orally twice a day) and human recombinant interferon alfa (150 IU orally every 24 hours) were administered and very successful results were obtained (Kahraman, 2019).

1.9.1. TREATMENT- II

Respiratory and gastrointestinal viruses such as feline calicivirus (FCV), feline herpesvirus (FHV-1), feline influenza virus, feline panleukopenia virus (FPV) and feline infectious peritonitis virus (FIPV) can be considered as the main causes of acute and chronic infections in cats. While some diseases caused by these viruses are brought under control with widespread vaccination programs, FIP due to FIPV remains a problem. Therefore, it is urgent to develop effective, safe and broad-spectrum antiviral drugs for viral diseases of cats. Today, the treatment methods used for FIP are still controversial. However, intensive research for the treatment of FIP disease continues uninterruptedly. In vitro studies have shown that the antimalarial drug with the active ingredient Mefloquine, which is used in the treatment of chloroquine-resistant malaria in

humans, is an effective antiviral drug in the prevention of FCoV and FCV replication. Inonotus obliquus polysaccharides (IOPs), also known as Chaga mushroom in humans, are used as a potential drug for the treatment and prevention of cancer, cardiopathy, diabetes, AIDS, pancreatitis and other diseases. Therefore, IOPs may be an effective and broad-spectrum antiviral drug against viral infections in cats. In addition, TNF-α and IFN-ɣ have important roles in the pathogenesis of FIPV infections and immune response in cats. In experimental FIP cases, the imbalance between some cytokines (increase in TNF-α and decrease in interferonɣ) is remarkable in the early period of infection. Interestingly, higher levels of IFN-ɣ were detected in FCoV-infected cats living in crowded environments such as shelters and showing no signs of disease compared to cats showing signs of FIP. This suggests that IFN-ɣ may play an important role in suppressing the infection. Omega feline recombinant interferon was found to inhibit viral replication of parvoviruses in dogs and was effective in the treatment of FeLV and FCoV infections. However, it is not clear whether feline recombinant interferon omega is effective in treating other viral infections of cats. In general, clinical findings of any disease are minimized by the use of corticosteroids and cyclophosphamide. Coadministration of feline interferon and glucocorticoids is considered a promising innovation. The main reason for the use of feline interferon is that cats with FIP cannot produce interferon

gamma. In this treatment, rFeIFN was administered subcutaneously at 1 MU/kg from baseline until remission, followed by weekly injections at the same dose, dexamethasone 1 mg/kg was administered once intrathorocically, prednisolone was continued orally at 2 mg/kg, gradually decreasing to 0.5 mg/kg, and as a result of this treatment, 4 out of 12 cats recovered completely (Baş and Ok, 2020).

There are various case reports on the positive effects of pentoxifylline (pentoxifyline; PTX), a Methylxanthine derivative used in the treatment of muscle pain due to peripheral arterial diseases, on the survival time of cats with FIP. Pentoxifylline inhibits the release of cytokines (especially TNF-alpha) and thus reduces the severity of vasculitis, preventing the risk of excessive effusion. This is suggested to contribute to the recovery of the disease in cats and causes an extension of lifespan. In the recommended protocol for the treatment of effusive or non-effusive FIP, 10-15 mg/kg pentoxifyline, PO, is given orally every 12 hours, 1.1 mg/kg prednisolone once daily and 150 units of interferon alpha orally. As known, pentoxifyline is used in the treatment of vascular and cerebrovascular diseases in which microvascular blood flow is suppressed. Further studies are needed to reveal the effectiveness of this drug in the treatment of FIP (Baş and Ok, 2020).

FIPV replication in macrophages/monocytes stimulates tumor necrosis factor (TNF)-alpha production. Considering that TNF-alpha production worsens FIP pathology, the effects of anti-feline TNF-alpha monoclonal antibody treatment were examined. Improvements in plasma alpha 1-glycoprotein and vascular endothelial growth factor levels and peripheral lymphocyte counts were determined after administration of anti-fTNF-alpha mAb to cats with FIP. These results suggested that anti-fTNF-alpha antibodies are effective in the treatment of FIP. The emergence of exotic diseases such as Ebola, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) in humans generated intense interest in drugs that inhibit RNA virus replication. Drugs that inhibit virus replication became the mainstay in the treatment of acute and chronic RNA and DNA virus infections of humans. Therefore, it was revealed that itraconazole (ITZ), which is well known as an antifungal agent and also has anticancer activity, inhibits viral RNA replication by targeting oxysterolbinding protein (OSBP) and OSBP-related protein-4 (ORP4). The combination of anti-human-TNF-alpha monoclonal antibody (ADA) and itraconazole (ICZ) is effective in cats with experimental FIP and should be considered as a treatment option until an effective antiviral drug becomes available in the veterinary field. U18666A is a cationic amphiphilic drug (CAD) that disrupts cholesterol biosynthesis and intracellular transport. U18666A inhibits

intracellular cholesterol biosynthesis by suppression of oxidosqualene cyclase. This drug also inhibits cholesterol release from lysosomes by disrupting the function of Niemann-Pick type C1 (NPC1), a cholesterol transporter. This drug was found to suppress the replication of Ebola virus, dengue virus and human hepatitis C virus. While U18666A strongly inhibited type 1 FCoV replication, it did not inhibit type II FCoV replication. In a recent experimental study investigating the in vivo antiviral effects of U18666A against type I feline infectious peritonitis, they administered U18666A to cats experimentally infected with type I FIPV and reported that it could suppress the development of FIP compared to the control group. However, it was concluded that the number of animals was too low to detect the antiviral effect of U18666A in cases with FIP. There are no current commercially available antiviral drugs and no known treatment algorithm for coronavirus infections in humans or animals. Therefore, it was determined that in vivo coronavirus replication is suppressed in principle by 3CLpro inhibition, and it was suggested that some 3CLpro inhibitors can be used as therapeutic agents against important viruses that cause serious diseases in cats. For this purpose, trial studies were conducted to create a treatment algorithm with GC376 in cats with effusive and nonfusive FIP. In a study conducted with this drug, 7 out of 20 cats with different forms responded to the treatment. Two side effects of GC376 were observed during this treatment. The first side effect was

deep localized ulceration on the skin due to continuous injection into the same area, and the second side effect was that the permanent teeth remained small in size. This study is the first antiviral drug trial considered for FIP. Another drug tested similar to the above study is the nucleoside analogue GS-441524. Due to its small molecular structure, it has an effect on the transcription mechanism. 31 cats diagnosed with probable FIP were treated for 12 weeks and 24 cats survived. The results obtained from the patients exceeded expectations and it was concluded that FIP is a treatable disease (Baş and Ok, 2020).

1.10. PROTECTION

When FCoV seropositive kittens aged 12-24 weeks were kept in the same environment with other cats of different ages, the incidence of the disease was determined to be 52%. However, it was 30% in kittens isolated in a separate place with the mother. In addition, 16-week-old kittens isolated alone at home without their mother remained seronegative. In this study, it was concluded that the disease is transmitted from the mother and mostly from other individuals. The main way to protect against FCoV is isolation, good nutrition, taking health precautions and ensuring hygiene. Many attempts were made to develop a FIP vaccine in cats. Although some were reported to show protection, only one product entered commercial production. A heat-sensitive FCoV strain that can

replicate at low temperatures of the upper respiratory tract but does not reproduce at systematic temperatures was developed. In the study, the survival rate was reported to be 85% in the study group and 17% in the control group. When administered intranasally, it strengthened local immunity by increasing IgA. However, vaccine-induced deaths were observed in FCoV positive cats. The current vaccine can be administered to cats over 16 weeks of age. The biggest ongoing contradiction in this regard is that FCoV-negative kittens may give erroneous (+) results during vaccination due to the gradual decrease in maternal antibodies at 4-6 weeks. It was observed that if cats with FIPV antibodies are experimentally administered FIPV, a severe form of the disease can occur despite the pre-existing antibody response. This mechanism, called "Antibody Mediated Enhancement (ADE)", is based on the fact that pre-existing antibodies facilitate the entry of FCoVs into macrophages. Compared to seronegative cats, the vast majority of antibody-positive cats developed disease in a short period of time and even died. This was attributed to the ACE reaction. Many effective and safe vaccine studies have become complicated due to the formation of ADE after vaccination. Therefore, vaccine administration is not recommended in FIP infections because it stimulates antibody-mediated development. However, antibody-mediated development in FCoV infections has only been shown

experimentally in laboratory strains and the situation in natural field strains is unknown (Baş and Ok, 2020).

CONCLUSION AND RECOMMENDATIONS

Two different serotypes have been identified for the virus, which is classified in the Alphacoronavirus genus within the Coronaviridae family. Apart from these classifications, Feline Coronavirus (FCoV) can be examined in 2 separate biotypes, low pathogenic feline enteric coronavirus (FECV: low virulence FCoV) and high pathogenic FIP (Feline Infectious Peritonitis) virus (FIPV: high virulence FCoV). The diagnosis and treatment of FIP is still very difficult and controversial. This is caused by the fact that the virulent coronavirus strain that causes FIP cannot be differentiated antigenically and genetically from other avirulent coronaviruses. Therefore, antemortem diagnosis of FIP remains challenging in clinical practice. In postmortem examination, immuno-histo-chemical diagnostic tests from biopsy samples are used as the standard diagnostic method of the disease. Recently, it has been suggested that sequence analysis differences between the S genes of FECV and FIPVs may be a diagnostic tool in the diagnosis of FIP. First of all, the diagnosis of clinical FIP cases is based on the cat's age, origin, physical examination and clinical findings. FIPV is transmitted to healthy animals through routes such as feces, urine and saliva of infected cats. FIPV virus is taken into the body via the

oro-nasal route. Mutation of FECVs to FIPV occurs during viral replication in monocyte/macrophage cells. The fact that the replication cycle of FCoVs is 10-100 times higher in macrophages, especially in cats with FIV, supports the claims that it increases the risk of spontaneous mutation. Other factors that are effective in clinical disease are the way the agent enters the body, its amount, age, various stress factors, an immunosuppressive disease affecting the immune system, and genetic susceptibility. There is no effective treatment or prevention method for FIP. The main goal of treatment is to alleviate the inflammatory response caused by the disease with supportive treatment. Thoracocentesis and abdominocentesis are recommended for cats with excessive fluid accumulation in the thorax and abdomen.

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