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Immune mechanisms in the pathogenesis of feline infectious peritonitis in renal tissue: Focus on lymphocytes and cytokines in effusive and non-effusive forms

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ABSTRACT

Feline infectious peritonitis (FIP) is a fatal systemic disease caused by a virulent biotype of feline coronavirus, characterized by complex and heterogeneous immune responses. This study aimed to comparatively evaluate renal histopathological alterations and immune profiles in effusive and non-effusive forms of FIP, with particular emphasis on cytokine expression, lymphocyte subsets, and apoptosis. Formalin-fixed, paraffin-embedded kidney tissues from 40 cats with immunohistochemically confirmed FIP (20 effusive, 20 non-effusive) were retrospectively analyzed. Renal lesions were semi-quantitatively scored using digital pathology, and immunohistochemistry was performed to assess IL-1, IL-6, TNF-α, CD8, CD19, and Caspase-3 expression. Effusive FIP was characterized by prominent vascular and exudative lesions, accompanied by significantly increased expression of proinflammatory cytokines (IL-1, IL-6, TNF-α) and higher $CD19^+$ B-cell immunoreactivity, consistent with a cytokine-driven, humoral-dominant immune response. In contrast, non-effusive FIP exhibited more localized granulomatous inflammation, increased $CD8^+$ T-cell infiltration, more pronounced interstitial fibrosis, and significantly higher Caspase-3 immunoreactivity, indicating enhanced apoptotic activity. Correlation analysis demonstrated no consistent positive association between $CD8^+$ T-cell density and Caspase-3 expression, suggesting that apoptosis in renal tissue is not solely mediated by cytotoxic T-cell activity. Furthermore, despite elevated TNF-α expression in effusive cases, Caspase-3 immunoreactivity remained relatively low, implying that alternative, potentially caspase-independent mechanisms of cell injury may predominate in this form. Overall, these findings indicate that effusive and non-effusive FIP are associated with distinct patterns of immune polarization and tissue injury rather than representing sequential stages of a uniform pathogenic process. Recognition of these divergent immunopathological profiles may contribute to improved interpretation of FIP lesions and support the development of targeted diagnostic and therapeutic strategies.

1. Introduction

Feline infectious peritonitis (FIP) is one of the most lethal and diagnostically elusive diseases in feline medicine. It results from infection with a virulent mutant biotype of feline coronavirus (FCoV), termed feline infectious peritonitis virus (FIPV), which arises from mutations particularly in the spike (S) protein within a commonly encountered enteric FCoV (Cony et al., 2024; Kipar and Meli, 2014). These mutations enable the virus to replicate within monocytes and macrophages, leading to systemic dissemination and profound immune dysregulation (Kennedy, 2020; Li et al., 2023). This transition from an enteric to a systemic infection underlies the pathogenesis of FIP and contributes to its complex clinical presentation and high mortality rate (Tekes and Thiel, 2016).

Clinically, FIP manifests in two primary forms: the effusive (wet) form, characterized by protein-rich serous effusions due to immune-mediated vasculitis, and the non-effusive (dry) form, marked by granulomatous or pyogranulomatous inflammation within parenchymal organs such as the kidneys, liver, central nervous system, and eyes (Kipar and Meli, 2014; Slaviero et al., 2024; Solikhah et al., 2024). However, emerging evidence suggests that these forms represent a spectrum of the same disease process, modulated by individual variations in host immune response rather than entirely distinct pathophysiological entities (Montali and Strandberg, 1972; Slaviero et al., 2024).

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Among the organs affected, the kidney is particularly susceptible in non-effusive FIP, where multifocal granulomatous nephritis constitutes a common and often severe lesion (Addie et al., 2004; McLeland et al., 2015). Despite this, few studies have directly compared renal pathology between the effusive and non-effusive forms of FIP. A systematic evaluation of lesion severity in both forms could offer valuable insights into the immunopathological mechanisms driving tissue-specific damage and aid in the development of improved diagnostic and prognostic strategies.

The immunopathogenesis of FIP involves a shift from protective cell-mediated immunity to an ineffective or even deleterious humoral response, driven by dysregulated interactions between FIPV-infected monocytes/macrophages and the host immune system (Kennedy, 2020; Stout et al., 2021). This imbalance is associated with elevated levels of proinflammatory cytokines particularly interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) which contribute to endothelial dysfunction, vascular leakage, and granulomatous inflammation (Dean et al., 2003; Dewerchin et al., 2005; Tekes and Thiel, 2016). Additionally, $CD8^+$ cytotoxic T cells are markedly depleted because of virus-induced lymphocyte apoptosis, leading to impaired cell-mediated immunity. At the same time, dysregulated B cell responses characterized by hyperactivation and excessive production of non-protective antibodies facilitate immune complex formation and disease progression through mechanisms such as antibody-dependent enhancement (Haagmans et al., 1996; Mustaffa-Kamal et al., 2019).

This study aimed to systematically evaluate the severity of renal lesions in both effusive and non-effusive forms of FIP and to investigate the immunological profiles associated with each clinical presentation. The study specifically focused on the spatial expression patterns of major proinflammatory cytokines and lymphocyte subsets to highlight their distribution within renal tissue and better understand their role in the immunopathogenesis of FIP.

2. Materials and methods

2.1. Animals and tissue samples

This retrospective study was conducted using archival formalin-fixed, paraffin-embedded renal tissue samples collected between 2016 and 2024 at the Department of Pathology, Faculty of Veterinary Medicine, Balıkesir University. The study group consisted of 40 domestic cats that had been submitted for necropsy and diagnosed with feline infectious peritonitis (FIP) based on clinical history, gross necropsy findings, and laboratory confirmation via both immunohistochemistry (IHC) and reverse transcriptase-polymerase chain reaction (RT-PCR). Of these, 20 cats had effusive FIP and 20 had non-effusive FIP. All cases presented with gross necropsy findings consistent with their respective forms. Classification of effusive and non-effusive FIP was based on gross necropsy findings using predefined pathological criteria. Cats presenting with at least four out of five characteristic necropsy features corresponding to either effusive or non-effusive FIP were assigned to the respective group. Mixed or transitional forms of feline infectious peritonitis were excluded from the study. Accordingly, cases showing gross necropsy features overlapping with the opposite form were not included to ensure strict form-based classification (Table 1) (Kipar and Meli, 2014; Solikhah et al., 2024). As this retrospective study was based exclusively on archived formalin-fixed, paraffin-embedded tissues and involved no procedures on live animals, ethical committee approval was not required.

2.2. Histopathology

Tissue samples were sectioned at 4 μm thickness and stained with Hematoxylin and Eosin (HE) for histopathological evaluation. Periodic acid–Schiff (PAS) staining was used to assess glomerular basement membranes, while Masson's trichrome (MT) staining was applied for the detection of interstitial fibrosis.

Table 1
Gross necropsy criteria used for classification of effusive (wet) and non-effusive (dry) forms of FIP.

Effusive (Wet) FIP	Non-effusive (Dry) FIP
1. Large volumes of protein- and fibrin-rich effusion in the abdominal and/or thoracic cavities 2. Diffuse fibrinous or fibrinopurulent polyserositis 3. Dull, opaque serosal surfaces covered with fibrin strands 4. Fibrin deposition and adhesions involving the omentum and mesentery 5. Widespread vasculitis-associated serosal exudation	1. Absence or minimal accumulation of serosal effusion 2. Nodular lesions in kidneys, liver, and mesenteric lymph nodes 3. Multifocal to coalescing pyogranulomatous lesions 4. White-gray plaques or nodules beneath organ capsules 5. Anterior uveitis

Renal lesions were graded semi-quantitatively using a structured scoring system adapted from (McLeland et al., 2015; Sethi et al., 2017). Five parameters were assessed: (1) glomerular alterations, (2) tubular degeneration/necrosis, (3) tubulointerstitial inflammation, (4) interstitial fibrosis, and (5) vascular lesions. Each category was scored from 0 (absent) to 3 (severe), based on the extent and distribution of lesions. For each cat included in the study, both the right and left kidneys were examined, and the mean of the two kidneys was used to generate a single composite score per case.

2.3. Immunohistochemistry (IHC)

Kidney tissue sections cut from paraffin blocks were stained by avidin–biotin–peroxidase method using primary antibodies against FIP (1/300, MCA2194 Bio-Rad), IL-1 (1/300, Bs-6319R Bioss), IL-6 (1/300, Bs-4539R Bioss), TNF-α (1/100, BT-AP15035 BT Lap), CD8 (1/100, K002374P Solarbio), CD19 (1/100, K003431P Solarbio), and Caspase 3 (1/200, ab13847 Abcam). Immunoreactivity was visualized using diaminobenzidine (DAB)/H_2O_2 and counterstained with Mayer's hematoxylin. Negative controls were prepared by replacing the primary antibody with PBS. The stained sections were examined under a light microscope, and representative images were captured using a digital camera. Immunopositive cells were quantified using QuPath (version 0.4.3). For each case and antibody, five images taken at 200× magnification were analyzed, and the mean number of positive cells was recorded as the final score.

2.4. Statistical analysis

All statistical analyses were performed using GraphPad Prism software (version X.0, GraphPad Software Inc., San Diego, CA, USA). The study population was divided into two groups based on clinical presentation: effusive ($n = 20$) and non-effusive ($n = 20$) forms of FIP. Data were first tested for normality using the Shapiro–Wilk test. For normally distributed data, comparisons between the two groups were made using the unpaired Student's *t*-test. The results were presented as graph displaying the median (line) and individual values. In addition, correlation analyses were conducted to assess the relationships between immunological markers using Spearman's rank correlation and Pearson's correlation tests, depending on data distribution. The results of these analyses are presented in the Supplementary Data.

3. Results

In the histopathological examination of the kidneys from cats with feline infectious peritonitis (FIP), a wide spectrum of renal lesions was observed, irrespective of clinical form. Tubular epithelial degeneration and necrosis were commonly encountered, often accompanied by luminal proteinaceous casts and varying degrees of interstitial edema.

Tubulointerstitial nephritis, characterized by lymphoplasmacytic infiltration, was a prominent finding and frequently extended into the corticomedullary junction. Glomerular changes, including mesangial matrix expansion and capillary tuft collapse, were noted in both forms, potentially reflecting immune complex deposition and chronic inflammatory injury (Fig. 1).

More specific features differed between the two clinical presentations. In the effusive form, vascular alterations were especially prominent, with endothelial swelling, perivascular fibrin deposition, and mild vasculitis frequently observed. Glomerular exudation was also more conspicuous in this form, indicating increased vascular permeability (Fig. 1c). Additionally, fibrin deposits, scattered neutrophils, and dense mononuclear cell infiltrations were observed, particularly in the subcapsular regions. In contrast, kidneys from cats with the non-effusive form showed more localized lesions, such as focal areas of coagulative necrosis surrounded by dense inflammatory infiltrates composed predominantly of macrophages, lymphocytes, and plasma cells, either encircling the necrotic foci or forming discrete perivascular aggregates (Fig. 1e–f). Necrotic foci associated with granulomatous inflammatory organization were observed in these localized lesions. These inflammatory cells often organized into granulomatous structures extending from perivascular regions into the surrounding parenchyma. Interstitial fibrosis was more pronounced in the non-effusive form, suggesting chronicity and progressive tissue remodeling (Fig. 1h). The scoring of these histopathological lesions is presented in Fig. 2.

In this study, kidney tissues from FIP diagnosed cats were evaluated immunohistochemically for the expression of IL-1, IL-6, TNF-α, CD8, CD19, and Caspase-3. Scoring of immunoreactivities was performed using software by counting immunopositive cells. The statistical evaluation of IHC scores is presented in Fig. 2.

In kidney tissues obtained from both clinical forms of feline infectious peritonitis (FIP), IHC staining for FIP antigen revealed distinct intracytoplasmic immunoreactivity localized within macrophages (Fig. 3). When the expression patterns of inflammatory cytokines were compared between the groups, a notable increase in IL-1 immunoreactivity was observed in the renal tissues of cats with the effusive form. This expression was predominantly cytoplasmic and appeared more widespread relative to the non-effusive form (Fig. 4). Similarly, IL-6 showed markedly stronger staining intensity in the effusive group, again with prominent cytoplasmic localization (Fig. 5). TNF-α immunoreactivity followed the same trend, with significantly higher expression levels and cytoplasmic distribution in the effusive cases compared to non-effusive ones (Fig. 6).

Regarding lymphocyte-associated markers, CD8 immunoreactivity was found to be reduced in the effusive form, indicating a possible suppression or redistribution of cytotoxic T-cell activity in this group (Fig. 7). Conversely, CD19 expression, a marker for B lymphocytes, was more pronounced in the effusive group, suggesting an enhanced humoral immune component (Fig. 8).

Apoptotic activity, as assessed by Caspase-3 expression, was also evaluated. In the effusive form, Caspase-3 immunoreactivity appeared lower in intensity and was predominantly confined to the cytoplasm, in contrast to the non-effusive form where stronger expression was detected (Fig. 9).

4. Discussion

Coronaviruses can cause a wide spectrum of diseases in both humans and animals, ranging from mild conditions such as common cold and diarrhea to severe and fatal infections (Şahinkesen et al., 2020). In cats, two distinct biotypes of coronaviruses are recognized: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV) (Li et al., 2023). FECV generally leads to mild, self-limiting enteritis or upper respiratory tract infections in kittens, while adult cats often recover from the infection without exhibiting any clinical symptoms. However, in approximately 5% of FECV-infected cats, mutations in the viral genome result in the emergence of FIPV, which causes feline infectious peritonitis (FIP). FIP is a fatal disease characterized by an Arthus-type immune-mediated reaction leading to effusions in body cavities, multiple organ failure, and neurological signs (Myrrha et al., 2011; Takano et al., 2011; Vogel et al., 2010).

FIP manifests in two clinical forms: effusive and non-effusive. The type of immune response elicited by the host determines the form that develops. A dominant humoral immune response favors the effusive form, whereas an active cell-mediated response results in the non-effusive form (Gao et al., 2023). In the effusive form, pyogranulomatous lesions are observed on the surfaces of organs within the thoracic and abdominal cavities, often accompanied by fibrin deposits and whitish plaques. In contrast, the non-effusive form lacks effusion, and lesions vary between cases, typically presenting as granulomas or pyogranulomas in the kidneys, lungs, liver, or central nervous system (Pedersen, 2009; Weiss and Scott, 1981). In the present study, histopathological examination of kidneys from cats with effusive FIP revealed capsular thickening due to mononuclear cell infiltration and fibrin accumulation, peri-capsular inflammatory infiltrates, and hydropic degeneration in proximal tubules near the cortex. In the non-effusive form, coagulative necrosis and perivascular mononuclear cell infiltration composed of macrophages, plasma cells, and lymphocytes were

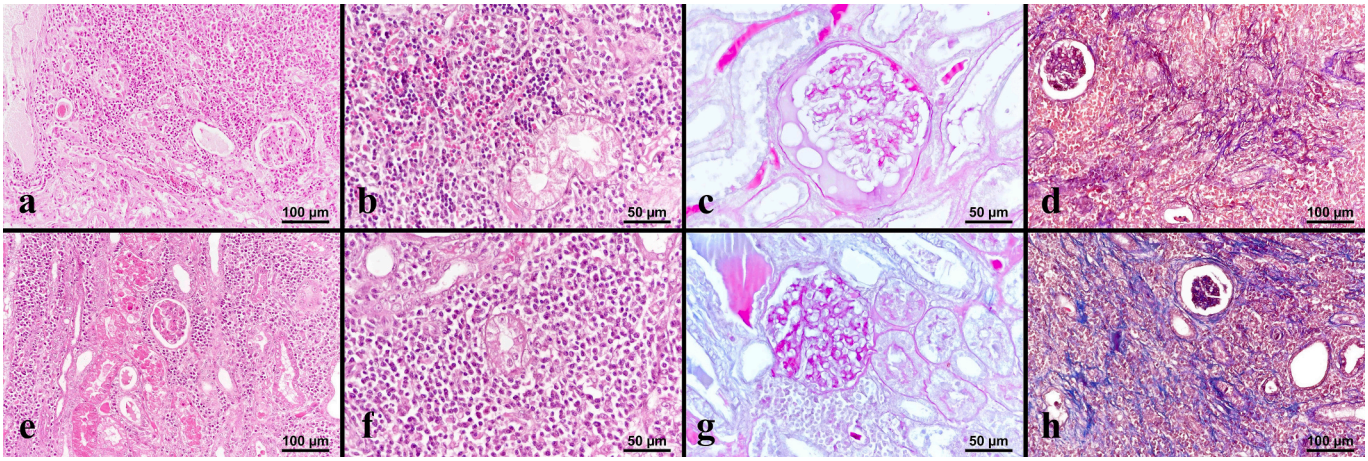

Fig. 1. Effusive form: (a–b) in the subcapsular region tubular degeneration and mononuclear cell infiltration (HE), (c) glomerular exudation (PAS), (d) mild interstitial fibrosis (MT). Non-effusive form: (e–f) tubular epithelial degeneration and necrosis, tubular dilatation, and mononuclear cell infiltration (HE). (g) Diffuse thickening of glomerular capillary walls and Bowman's capsule (PAS), (h) moderate interstitial fibrosis (MT).

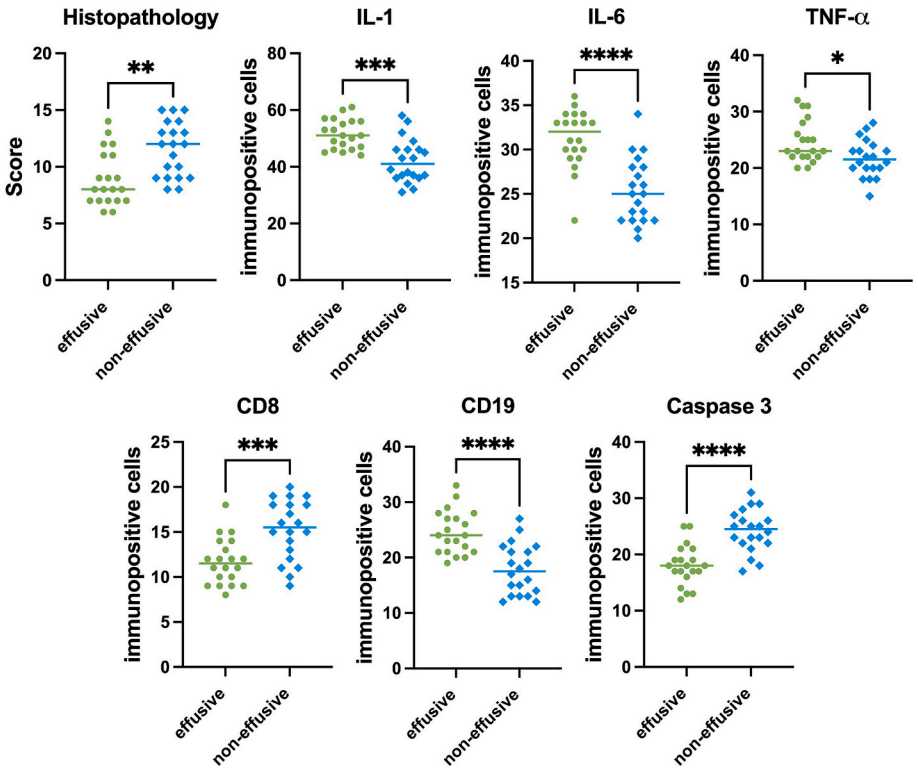

Fig. 2. Histopathological scoring of renal tissues from cats with effusive and non-effusive FIP findings and expression levels of IL-1, IL-6, TNF-α, CD8, CD19, and Caspase 3, in these tissues, assessed through IHC analysis and statistical evaluation. Data are presented as median (central line) with individual values. Statistical comparisons were performed using the Student's *t*-test (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$).

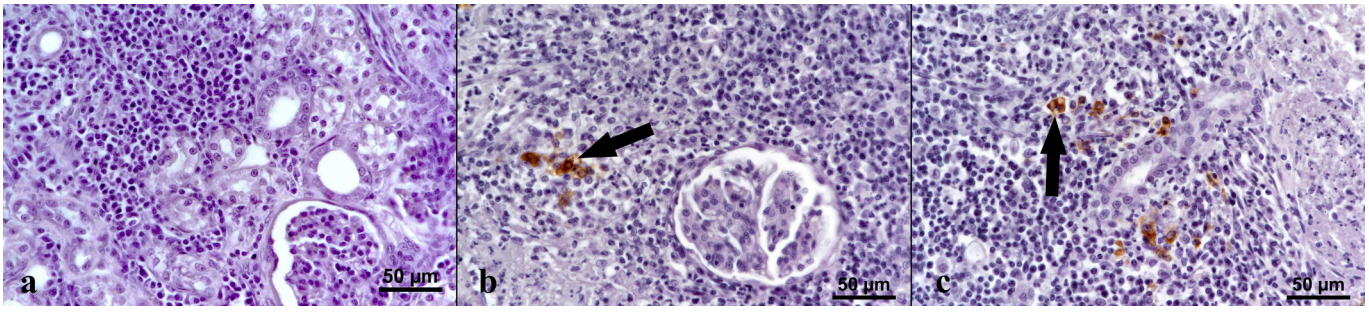

Fig. 3. FIP immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. Immunopositive reactions are observed in the cytoplasm of macrophages (arrows). IHC.

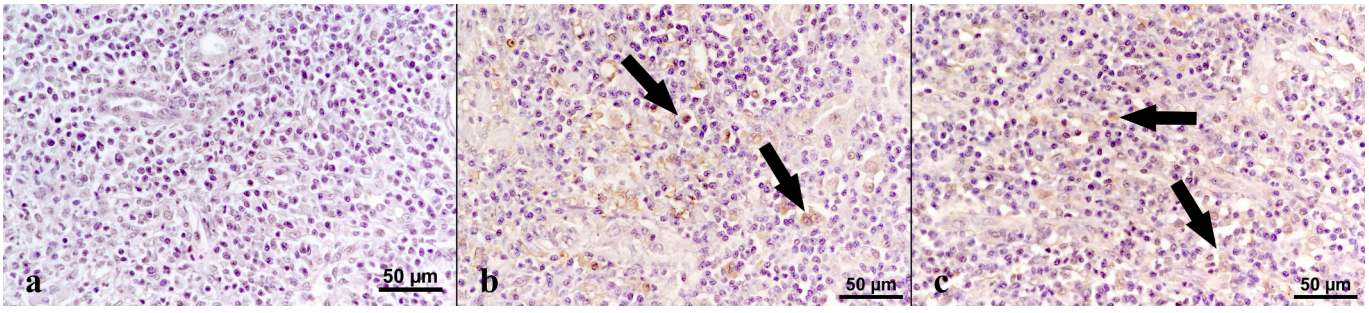

Fig. 4. IL-1 immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. The effusive form exhibits stronger immunopositive reactions (arrows) compared to the non-effusive form. IHC.

identified. These findings were consistent with previously published studies.

FIPV-infected monocytes and macrophages play a crucial role in the development of these lesions (Haijema et al., 2007). FIPV has a primary tropism for monocytes and macrophages, infecting and continuing to replicate within their cytoplasm (Regan et al., 2009). Activated

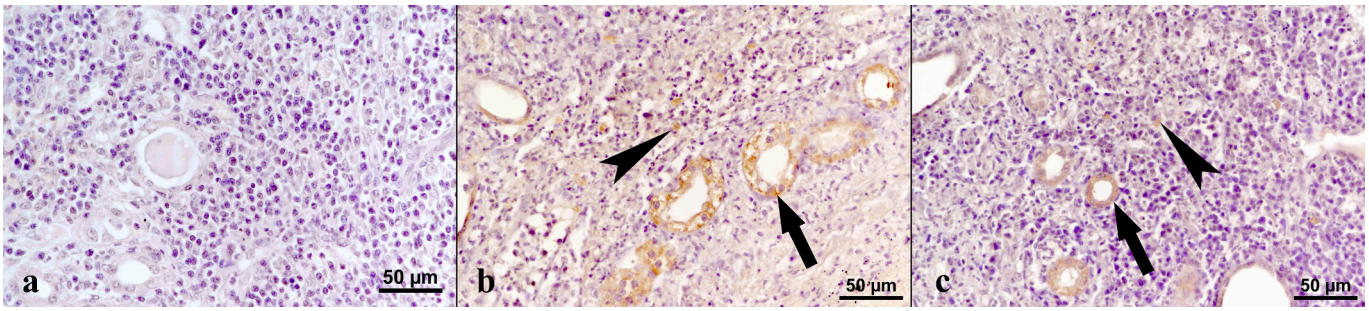

Fig. 5. IL-6 immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. In the effusive group, higher levels of cytoplasmic immunopositive reactions are observed in tubular epithelial (arrows) and inflammatory cells (arrowhead). IHC.

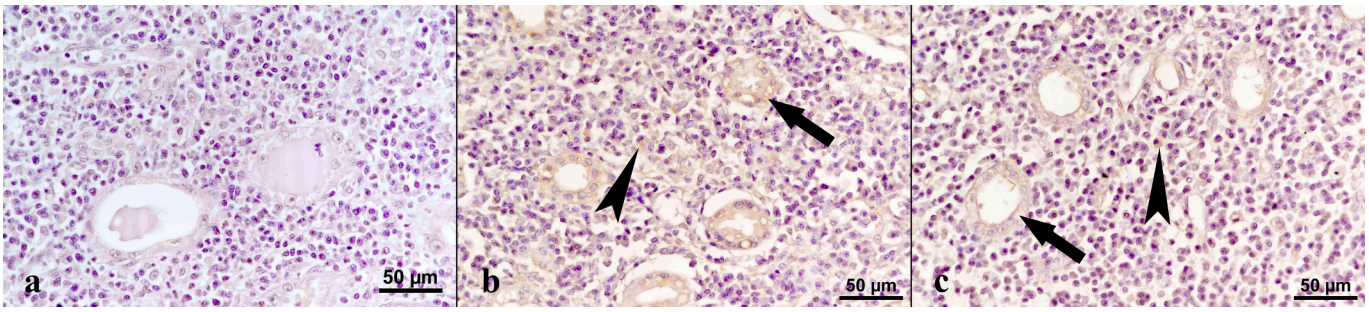

Fig. 6. TNF-α immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. In the effusive group, higher levels of cytoplasmic immunopositive reactions are observed in tubular epithelial (arrows) and inflammatory cells (arrowhead). IHC.

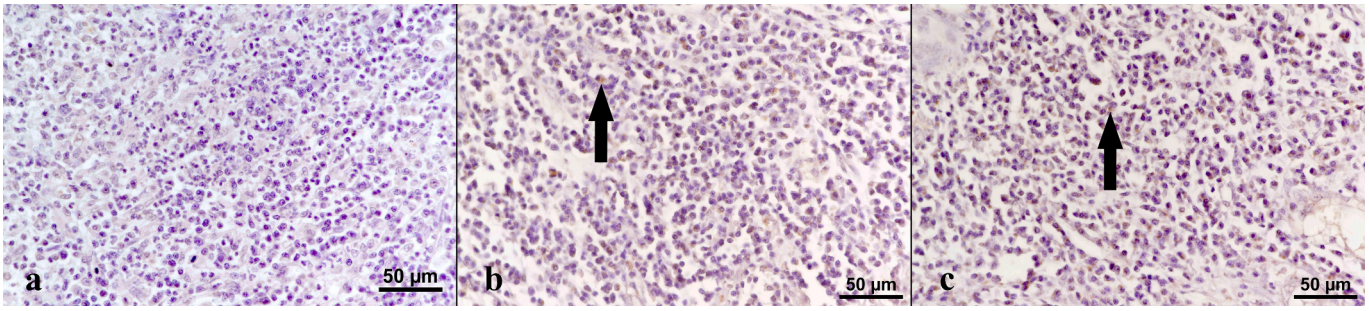

Fig. 7. CD8 immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. CD8 immunoreactivity is more prominent (arrow) in the non-effusive form, with a greater number of positive cells (arrow) than in the effusive form. IHC.

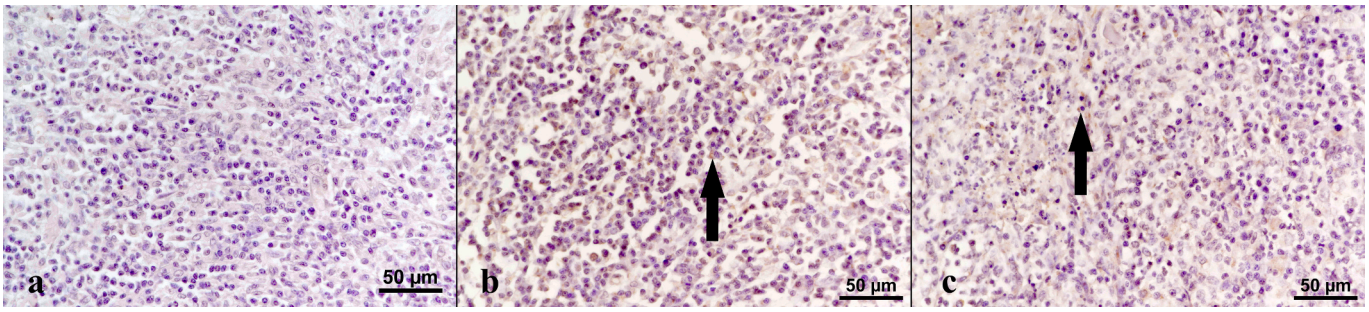

Fig. 8. CD19 immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. CD19 immunoreactivity is more pronounced in the effusive form (arrow), with a greater number of positive cells (arrow) than in the non-effusive form. IHC.

monocytes in circulation secrete pro-inflammatory cytokines such as TNF-α and IL-1 (Kipar et al., 2005). In addition to these cytokines, vascular endothelial growth factor (VEGF), also produced by infected monocytes and macrophages, is reported to increase vascular permeability and contribute to effusion formation (Takano et al., 2011). Several studies on naturally infected cats have demonstrated increased expression levels of IL-1, IL-6, and TNF-α in FIP cases (Kipar et al., 2005; Kiss et al., 2004). In the present study, the expression of these pro-inflammatory cytokines was investigated immunohistochemically in renal tissues from cats with effusive and non-effusive FIP. It was found

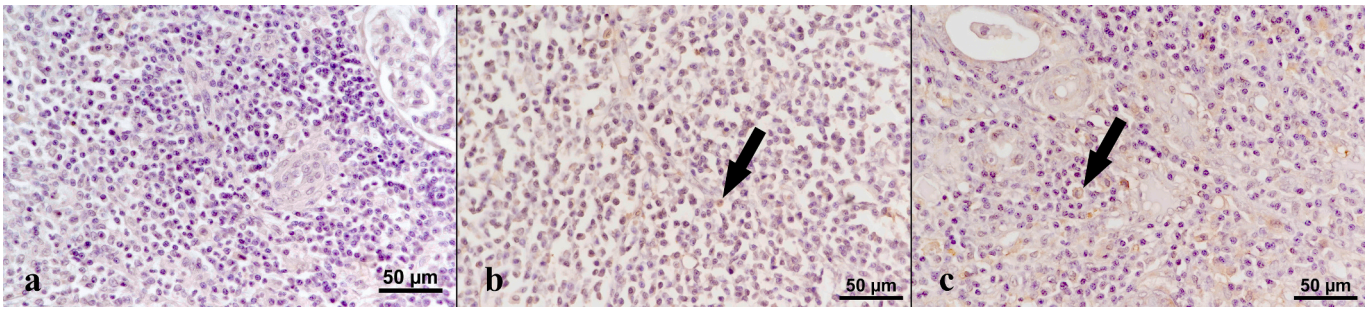

Fig. 9. Caspase-3 immunoreactivity in renal tissue: (a) Negative control, (b) effusive form, (c) non-effusive form. In the non-effusive form, Caspase-3 immunoreactivity appears more intense in the inflammatory cells compared to the effusive form (arrows). IHC.

that IL-1, IL-6, and TNF-α expressions were significantly higher in the kidneys of cats with the effusive form compared to those with the non-effusive form ($P < 0.05$).

IL-1, IL-6, and TNF-α are key drivers of the cytokine storm and play a pivotal role in disrupting vascular homeostasis. IL-1β and TNF-α activate endothelial cells by upregulating adhesion molecules and promoting NF-κB-mediated junctional disruption, while IL-6 enhances vascular permeability through cytoskeletal reorganization and increased VEGF production (Fajgenbaum and June, 2020; Tang et al., 2021). These cytokines synergistically induce endothelial leakage, facilitating the accumulation of protein-rich exudates. Their excessive activation may result in widespread tissue damage, multi-organ dysfunction, and death (Hu et al., 2021; Jarczak and Nierhaus, 2022). Based on these findings, it is plausible that IL-1, IL-6, and TNF-α contribute to the formation of abdominal and thoracic effusions observed in the effusive form of FIP.

In the pathogenesis of FIP, both the cytokines and the immune cells they activate are of critical importance. Cytokines released during infection activate monocytes, macrophages, lymphocytes, and plasma cells, initiating the immune response. The type of immune response mounted by the host determines the clinical form of the disease. A humoral-dominant response results in the effusive form, whereas a cell-mediated response leads to the non-effusive form (Gao et al., 2023; Pedersen, 2009). In the present study aimed to assess the type of immune response by comparing the expression levels of $CD8^+$ cytotoxic T cells and $CD19^+$ B cells in the renal tissues of cats with effusive and non-effusive FIP using immunohistochemistry. The results showed that CD8 expression was significantly lower, whereas CD19 expression was significantly higher in the effusive form compared to the non-effusive form ($P < 0.05$). Thus, B lymphocytes predominated in the effusive form, while T lymphocytes were more prominent in the non-effusive form.

In a previous study involving naturally and experimentally infected cats, it was reported that $CD8^+$ cytotoxic T cells activation occurred mainly in the late stages of infection and that early recovering animals exhibited minimal CD8 activity. Upon reinfection, however, these cells became activated (Mustaffa-Kamal et al., 2019). In our study, $CD8^+$ cytotoxic T cells were identified in the renal tissues of all cats, regardless of clinical form. This likely reflects the fact that all samples were obtained postmortem from naturally infected animals.

Other studies emphasize the pivotal role of $CD8^+$ cytotoxic T cells in the immune response against FIP, noting their ability to recognize and eliminate infected cells, thereby controlling infection and limiting disease progression (Mustaffa-Kamal et al., 2019). Based on these insights, the relatively low CD8 activity observed in our effusive group may reflect insufficient cellular immunity. Moreover, since $CD8^+$ cytotoxic T cells induce apoptosis via perforin and granzyme-mediated activation of caspase pathways, they may also contribute to tissue injury (Mustaffa-Kamal et al., 2019). Supporting this, we observed that necrosis and degeneration were more prevalent in non-effusive cases, which showed higher CD8 expression.

$CD19^+$ B cells, a subpopulation of B cells, play an important role in regulating immune responses. In FIP, these cells are involved in antibody production and the generation of humoral immunity. Although antibodies produced by B cells can help identify and eliminate infected cells, excessive antibody production and immune complex formation may worsen the disease (Kurosaki et al., 2015; Mustaffa-Kamal et al., 2019). Other studies have reported that FIPV-infected macrophages stimulate B cells to differentiate into plasma cells (Takano et al., 2009) and that B cell numbers are elevated in the effusive form (Pedersen, 2014, 2009). Consistent with these reports, our study found significantly higher CD19 expression in the effusive form compared to the non-effusive form ($P < 0.05$).

Although FIP is known to induce apoptosis, the exact role of apoptosis in its pathogenesis remains unclear (Shuid et al., 2015). Apoptosis is regulated by Caspases, which are classified into initiator and effector enzymes (Boatright and Salvesen, 2003). Effector Caspases, such as Caspase-3, are responsible for executing the apoptotic program by promoting membrane blebbing and cellular disassembly (Choudhary et al., 2015; Eskandari and Eaves, 2022). Studies investigating Caspase-3 expression in the kidneys of FIP-affected cats are limited. In this study, we evaluated apoptosis by assessing Caspase-3 expression in the kidneys of cats with effusive and non-effusive FIP. Caspase-3 immunoreactivity was found to be significantly higher in the non-effusive group than in the effusive group ($P < 0.05$), indicating that controlled cell death plays a more prominent role in the non-effusive form.

Apoptosis, largely mediated by caspase-dependent pathways, is considered an important component of (FIP) pathogenesis, although its precise contribution to tissue injury remains incompletely understood (Kennedy, 2020; Kipar and Meli, 2014). In the present study, Caspase-3, the key executioner caspase, showed significantly higher immunoreactivity in renal tissues from cats with the non-effusive form of FIP, indicating enhanced apoptotic activity in this clinical presentation. Correlation analysis revealed a significant negative association between $CD8^+$ T-cell immunoreactivity and Caspase-3 expression in the effusive form, whereas no significant correlation was observed in the non-effusive form. These findings suggest that $CD8^+$ T-cell infiltration does not uniformly translate into increased Caspase-3–mediated apoptosis and that the relationship between cytotoxic T cells and apoptotic signaling differs between clinical forms of FIP. $CD8^+$ cytotoxic T cells are known to induce target cell death through perforin- and granzyme-dependent mechanisms, which may activate caspase cascades but can also proceed via caspase-independent pathways (Reina-Campos et al., 2021). Furthermore, Caspase-3 immunoreactivity likely reflects apoptotic activity in a heterogeneous population of renal parenchymal and inflammatory cells rather than being restricted to $CD8^+$ T-cell target cells. The use of end-stage necropsy material may further obscure temporal relationships between immune cell infiltration and downstream apoptotic signaling. Notably, despite elevated TNF-α expression in the effusive form, Caspase-3 immunoreactivity was relatively lower, and no significant correlation was observed between these markers, suggesting that apoptotic pathways may not represent the predominant mechanism of cell injury and that alternative, potentially caspase-independent

mechanisms of cell death could contribute to renal tissue damage in this clinical presentation.

5. Conclusion

In conclusion, this study reveals distinct immunopathological patterns in the renal tissue of cats affected by effusive and non-effusive forms of feline infectious peritonitis. The effusive form is characterized by pronounced vascular alterations, elevated proinflammatory cytokine expression (IL-1, IL-6, TNF-α), and increased $CD19^+$ B-cell infiltration, supporting a cytokine-driven, humoral-dominant immune response. In contrast, the non-effusive form exhibits more localized granulomatous lesions, higher $CD8^+$ T-cell presence, and increased Caspase-3 immunoreactivity, indicating enhanced apoptotic activity.

Importantly, the lack of a significant correlation between $CD8^+$ T-cell density and Caspase-3 expression suggests that apoptosis in non-effusive FIP is not solely mediated by cytotoxic T-cell mechanisms but likely reflects complex, cell type–independent apoptotic processes within renal tissue. Furthermore, despite elevated TNF-α levels in the effusive form, lower Caspase-3 expression implies that non-apoptotic or caspase-independent pathways of cell injury may predominate in this clinical presentation.

Collectively, these findings underscore that the clinical manifestation of FIP is shaped by differential immune polarization rather than linear immune-effector pathways. Future studies integrating temporal analysis and molecular profiling of multiple cell death mechanisms are warranted to further elucidate the immunopathogenesis of FIP and to identify potential targets for therapeutic intervention.

CRediT authorship contribution statement

Mustafa Usta: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Funding acquisition, Data curation. **Asım Ayaz:** Methodology, Investigation, Formal analysis. **Muhammed Yusuf Kurban:** Visualization, Investigation, Data curation. **Musa Karaman:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no conflicts of interest related to the research, authorship, or publication of this article, including any affiliations with materials, methods, or commercial entities mentioned herein.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rvsc.2026.106142.

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