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RESEARCH ARTICLE

Histopathological and immunohistochemical findings in different tissues of goats infected with small ruminant lentivirus

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Küçük ruminant lentivirusu ile enfekte keçilerin farklı dokularındaki histopatolojik ve immunohistokimyasal bulguları

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Öz

Amaç: Küçük ruminant lentivirus enfeksiyonu, koyun ve keçilerde patolojik ve klinik olarak mastitis, maedi, visna ve artritise neden olan bir dizi ana hedef organı aynı anda ve immunpatojenik olarak etkileyebilen kronik ve tedavi edilemez bir karaktere sahiptir. Bu çalışmanın amacı, histopatolojik ve immunohistokimyasal olarak enfekte keçilerin farklı dokularındaki lezyonları ve hücresel dağılımını ortaya koymaktır.

Gereç ve Yöntem: Çalışmada, seropozitif olduğu bilinen toplam 6 adet keçi, ayrıca 1 adet abort fötus kullanıldı. Histopatolojik bulgular ve immunohistokimyasal olarak, hücresel dağılımlar tespit edildi.

Bulgular: Histopatolojik olarak bronkopnömoni ve kronik intersitisyel pnömoni, enteritis, böbreklerde proksimal ve distal tubulus epitellerinde hidropik dejenerasyon ve nekroz, hiyalin damlacıkları ve hiyalin silindirleri, dalakta konjesyon ve lenfoid hücrelerde azalma, kalpte konjesyon, hiyalin dejenerasyonu ve nekroz ile karaciğerde hidropik dejenerasyon, nekroz ve hepatitis gözlendi. İmmunohistokimyasal olarak akciğerde bronş ve bronşiyollerin epitellerinde, alveoler makrofajlarda ve lenfositlerde, dalakta lenfosit ve makrofajlarda, bağırsaklarda kript ve villus epitellerinde, lenfosit ve makrofajlarda, karaciğerde ise Kupffer hücrelerinde ve lenfositlerde pozitif boyanmalar görüldü. Aksine, böbrekler ve kalpte pozitiflik görülmedi.

Öneri: Sonuç olarak, keçi yetiştiriciliğinde önemli bir yeri bulunan küçük ruminant lentivirus enfeksiyonunda elde edilen veriler ve bu verilerin, yeni çalışmalarda ve geliştirilebilecek mücadele programlarında önem arz edeceği düşünülmektedir.

Anahtar kelimeler: Histopatoloji, immunohistokimya, keçi, küçük ruminant lentivirus

Abstract

Aim: Small ruminant lentivirus infections has chronic and incurable character that might simultaneously and immunopathogenically affect several major target organs, causing pathological and clinical mastitis, maedi, visna, and arthritis in sheep and goats. This study aimed to reveal the lesions and their cellular distribution in different tissues of histopathologically and immunohistochemically infected goats.

Materials and Methods: A total of six goats, known as seropositive, and one aborted fetus, were used for the study. Histopathologic findings and immunohistochemical cellular distributions were determined.

Results: Histopathologically, bronchopneumonia and chronic interstitial pneumonia, enteritis, hyaline droplets and hyaline cylinders, hydropic degeneration and necrosis of proximal and distal tubular epithelium in the kidneys, congestion and decrease of lymphoid cells in the spleen, congestion, hyaline degeneration and necrosis in the heart, and hydropic degeneration, necrosis and hepatitis in the liver were observed. Immunohistochemically, positive staining was observed in the epithelium of the bronchi and bronchioles, alveolar macrophages and lymphocytes in the lung, lymphocytes and macrophages in the spleen, crypt, and villous epitelium, lymphocytes and macrophages in the intestine, and Kupffer cells and lymphocytes in the liver. In contrast, no positivity was observed in the kidneys and heart.

Conclusion: It is anticipated that the data obtained on small ruminant lentivirus infections will have an important place in goat breeding and will be important for new studies and control programs that may be developed.

Keywords: Goat, histopathology, immunohistochemistry, small ruminant lentivirus

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Introduction

Small ruminant lentiviruses (SRLVs) are enveloped, single-stranded RNA viruses belonging to the *Retroviridae* family's *lentivirus* genus. Two different viruses are involved, *Maedi-Visna* virus (MVV) in sheep and *Caprine arthritis encephalitis virus* (CAEV) in goats (Blacklaws et al 2004, Ramirez et al 2013, Tu et al 2017, de Miguel et al 2021, Hailat et al 2022). SRLV can overcome the interspecific barrier and spread from sheep to goats and vice versa. Because the mammary gland is the main target tissue for the virus, kids and lambs become infected early in life by ingesting colostrum and milk from their infected mothers (East et al 1993, Storset et al 1997, İnce 2020, Alamerew et al 2022). Infection of the endometrium and detection of proviral DNA in reproductive tissues such as the ovary and fallopian tube have focused on transplacental or intrauterine vertical contamination (Ali 1987, Fieni et al 2003, Peterhans et al 2004, Konishi et al 2011, Rodrigues et al 2017, Tu et al 2017).

Small ruminant lentiviruses cause a chronic, incurable infection that can simultaneously and immunopathogenically affect some major target organs, including the lungs, central nervous system, mammary gland, bone marrow, uterus, epididymis, and joint tissues in sheep and goats, causing multisystemic inflammatory infection of a degenerative character (Blacklaws et al 2004, Brellou et al 2007, McNeilly et al 2008, Ramirez et al 2013, Minguijon et al 2015). It is also reported that pathological changes may occur in other organs, such as the kidney, liver, and heart (Blacklaws et al 2004).

Due to the persistent nature of SRLV infection, seropositivity is sufficient to detect infected animals (IE 2018). Given this information, there are two different approaches to determining infection. The first is the serological diagnosis in live animals, and the other is the use of necropsy tissue (OIE 2018). In Türkiye, there are many serological studies on the epidemiology of SRLV infections in sheep and goats (Burgu et al 1990,imtay et al 2004, Ataseven et al 2006, Albayrak et al 2012, Yavru et al 2012, Özkan et al 2014, Ün et al 2018) and few virological studies (Tan and Alkan 2002, Bertolotti et al 2011, Muz et al 2013, Doğanet al 2021). However, only one study has been reported on the histopathological diagnosis of the infection (Eroksuz et al 2022). This study aimed to reveal the cellular distribution of small ruminant lentivirus in tissues of chronically infected goats by histopathological and immunohistochemical techniques.

Material and Methods

Animal materials

In this study, some organs (lung, liver, heart, intestine, kidney, and spleen) of six goats that were found to be seropositive in the previous study (Doğanet al 2021) using a commercial ELISA kit (IDEXX MVV/CAEV P28 Antibody Screening Test Kit, Version, Switzerland) and reported to have been cut a few weeks later by Veli İncecik due to cachexia, lameness, and respiratory distress on history taking, and an aborted material were also examined. The commercial dairy goat herd taken the tissue samples for pathological examination were certified as free from major diseases (e.g. brucellosis and tuberculosis) by the Ministry of Agriculture and Forestry of the Republic of Türkiye. However, no positive sample was discovered in all tissue samples in the particular PCR amplification done using the primer pair (synthetic oligonucleotide sequences) for the virus's 5'UTR gene region reported by Vilcek et al. (Vilcek et al 1994) for pestivirus nucleic acid.

Histopathologic analysis

Tissue samples from the goats (lung, liver, heart, intestine, kidney, and spleen) were fixed in 10% formalin solution, and paraffin-embedded blocks were obtained after routine tissue examination. Sections of 5 µm thickness were obtained from the tissue samples. After staining with hematoxylin-eosin (HE) (Luna 1968), they were examined under a binocular light microscope (lympus BX50F, Tokyo, Japan).

Immunohistochemistry

For immunohistochemical examination, 5 µm thick sections were cut from the tissue paraffin-embedded blocks of the specimens on positively charged slides. The prepared sections were stained with CAEV hyperimmune serum obtained in the Department of Virology using the combination method of microwave antigen retrieval and streptavidin-biotin peroxidase. After washing with PBS, slides were stained with DAB chromogen (DAK, Glostrup, Denmark) for 7 minutes, followed by 1 minute with Mayer's haematoxylin (Thermo Fisher Scientific, NY, USA) for counterstaining. For CAEV assessment, the number of positively stained cells was determined at 400× magnification in 10 consecutive fields and scored semi-quantitatively (0: no stained cells; point 1: 1-10 positively stained cells; point 2: 11-20 positively stained cells; point 3: > 20 positively stained cells). Microscopic images of the specimens were taken under a light microscope (lympus BX50F, Tokyo, Japan).

Results

Histopathologically, thickening in the interalveolar septum due to mononuclear cell infiltration with a majority of lymphocytes were noted in two of the lung tissue samples. Intracytoplasmic inclusion was also observed in the alveolar epithelium. Alveolar edema was noted in only one of these lungs (Figure 1A). In other goat lung tissue samples, thickening due to mononuclear and a few neutrophil

granulocyte infiltrations with a majority of lymphocytes in the interalveolar septum were seen. Also, neutrophil granulocyte infiltrations and alveolar macrophages in the alveoli, smooth muscle hypertrophy around the bronchi and bronchioles, and mononuclear cell infiltrations were observed (Figure 1B). In addition, degeneration of the bronchiolar epithelium and desquamation of the epithelium due to necrosis were observed in a goat lung (Figure 1C). In addition, intracytoplasmic inclusion bodies were observed in bronchial and bronchiolar epithelium (Figure 1D). Severe emphysema was noted in only two lung tissues. In aborted goat lungs, thickening and congestion were observed in the vessels due to infiltration with mononuclear cells in the interalveolar septum.

It was observed that sinusoids were filled with erythrocytes, lymphoid cells decreased, and macrophages increased in the spleen (Figure 2A). Hydropic degeneration and necrosis in the hepatocytes, as well as an increase in Kupffer cells, were observed in three livers (Figure 2B). In comparison, congestion and mild fatty vacuoles were seen in hepatocytes in two livers. Mononuclear cell and macrophage infiltrations with predominantly lymphocytes were noted in only two livers. In the kidneys, congestion, hydropic degeneration, and necrosis were observed in the proximal and distal tubular epithelium in three of them. At the same time, hyaline droplets and hyaline cylinders were noted in two kidneys (Figure 2C). Hyperemia, hyaline degeneration and necrosis were observed in the heart (Figure 2D). Mononuclear cell infiltrations consisting of lymphocytes and macrophages were observed in the lamina propria of the intestine (Figure 2E), as well as degeneration in some crypts; hyperplasia was noted in some crypts. Intracytoplasmic inclusions were noted in the crypt epithelium of two goat intestines (Figure 2F). In addition, degeneration and desquamation of the lamina epithelialis and hyperemia of the submucosa were observed in both goat intestines. Because of autolytic changes were noted in the macroscopically softened and dispersed brain samples, they could not be pathologically examined.

Immunohistochemically, positive staining was detected in the lungs, spleen, intestine, and liver, but no staining was detected in the kidneys and heart (Table 1). In the lungs, positive reactions were detected in the epithelium of bronchi and bronchioles, in alveolar macrophages, and the cytoplasm of lymphocytes and macrophages in the interalveolar septum (Figure 3A-B). Positive staining was observed in the spleen, especially in lymphocytes and macrophages (Figure 3C-D). In the intestine, positive reactions were noted mainly in the crypt and villous epithelium, lymphocytes, and macrophages (Figure 3E). It was detected mainly in Kupffer cells but also in sinusoids and lymphocytes in the liver (Figure 3F). No positivity was detected in the kidneys and heart. The intensity of immunohistochemical staining in the cells is detailed in Table 2.

Table 1. Results of immunohistochemical staining of organs

	IHC						
	Lung	Spleen	Intestines	Liver	Kidney	Heart	Brain
Goat 1	+	+	+	+	-	-	NE
Goat 2	+	+	+	+	-	-	NE
Goat 3	+	+	+	+	-	-	NE
Goat 4	+	+	-	-	-	-	NE
Goat 5	+	+	+	+	-	-	NE
Goat 6	+	+	+	+	-	-	NE
Abortion	-	+	-	-	-	-	NE

NE: Not examined

Table 2. The intensity of immunohistochemical staining in cells

	Lung		Spleen	Intestines		Liver	
	Bronchi/ bronchiolar epithelium	Lymphocyte/ Macrophage	Lymphocyte/ Macrophage	Crypt/villus epithelium	Lymphocyte/ Macrophage	Hepatocyte	Lymphocyte /Kupffer Cells
Goat 1	++	++	+	++	+	-	++
Goat 2	+	++	+	++	+	-	++
Goat 3	+++	+++	++	+++	++	-	+++
Goat 4	+	+	+	-	-	-	-
Goat 5	+	+	+	+	+	-	+
Goat 6	++	++	++	+	+	-	++
Abortion	-	-	+	-	-	-	-

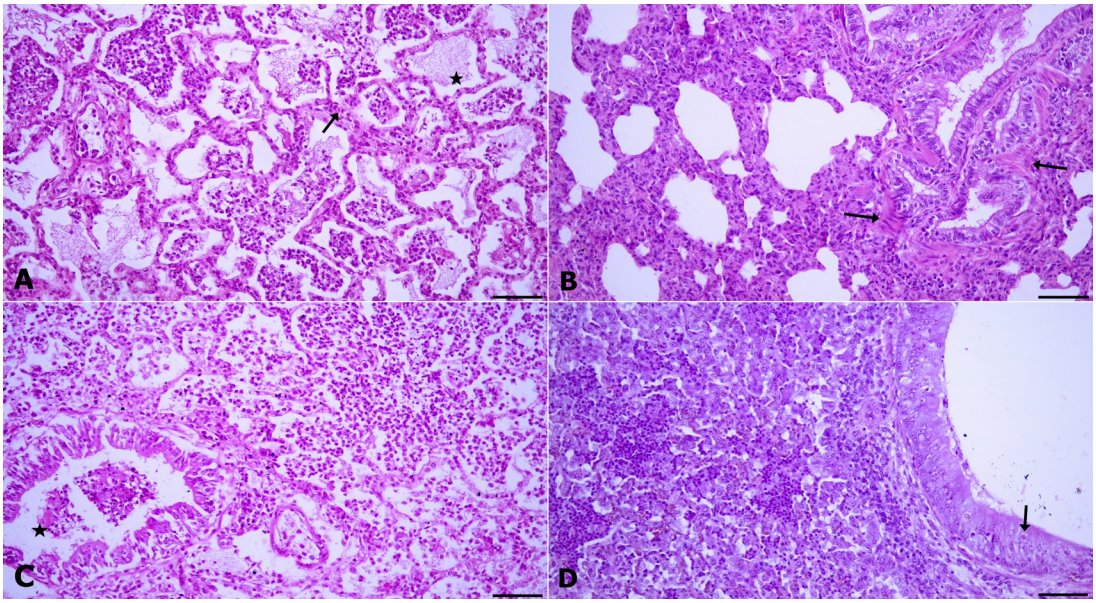

Figure 1. Histopathology of lung. A) Intracytoplasmic inclusion (arrow), oedema (asterix) and degeneration and desquamation in pneumocytes, B) Thickening due to alveolar macrophages and mononuclear cells in the interalveolar septum, smooth muscular hypertrophy around the bronchioles (arrows), C) Mononuclear cells and few neutrophil granulocyte infiltrate in alveoli, degeneration and desquamation in bronchioles (asterix), D) Neutrophil granulocyte infiltration in the alveoli and intracytoplasmic inclusion bodies in the bronchioles (arrow), HE. Bar= 100 µm (A-D).

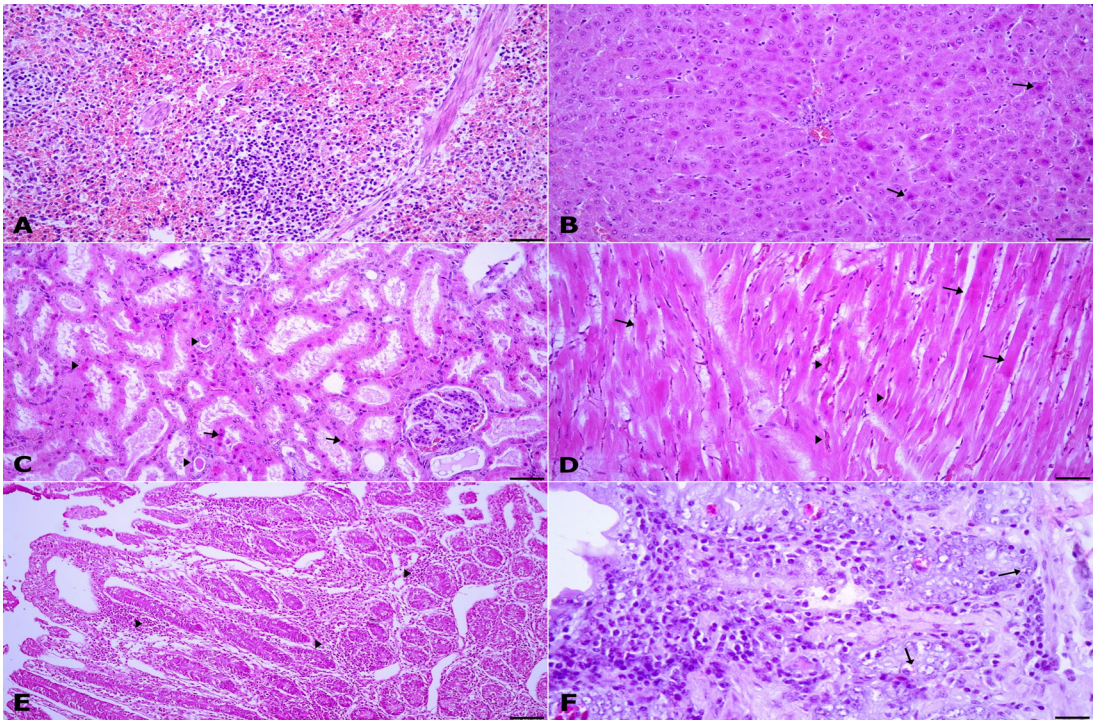

Figure 2. Histopathology of spleen, liver, kidney, heart and intestines. A) Congestion in red pulp and decrease in lymphoid cells, spleen. B) Necrosis in hepatocytes (arrows) and hyperplasia in Kupffer cells, liver. C) Degeneration and necrosis in proximal tubules (arrows), hyaline droplets and hyaline cylinders (arrowheads), kidney. D) Hyperemia (arrowheads), hyaline degeneration and necrosis (arrows), heart. E) Degeneration and desquamation in the epithelium, mononuclear cell infiltration in the propria (arrowheads), intestine. F) Intracytoplasmic inclusion in the crypt epithelium (arrows), intestine, HE. Bar= 50 µm (F), 100 µm (A-D), 200 µm (E).

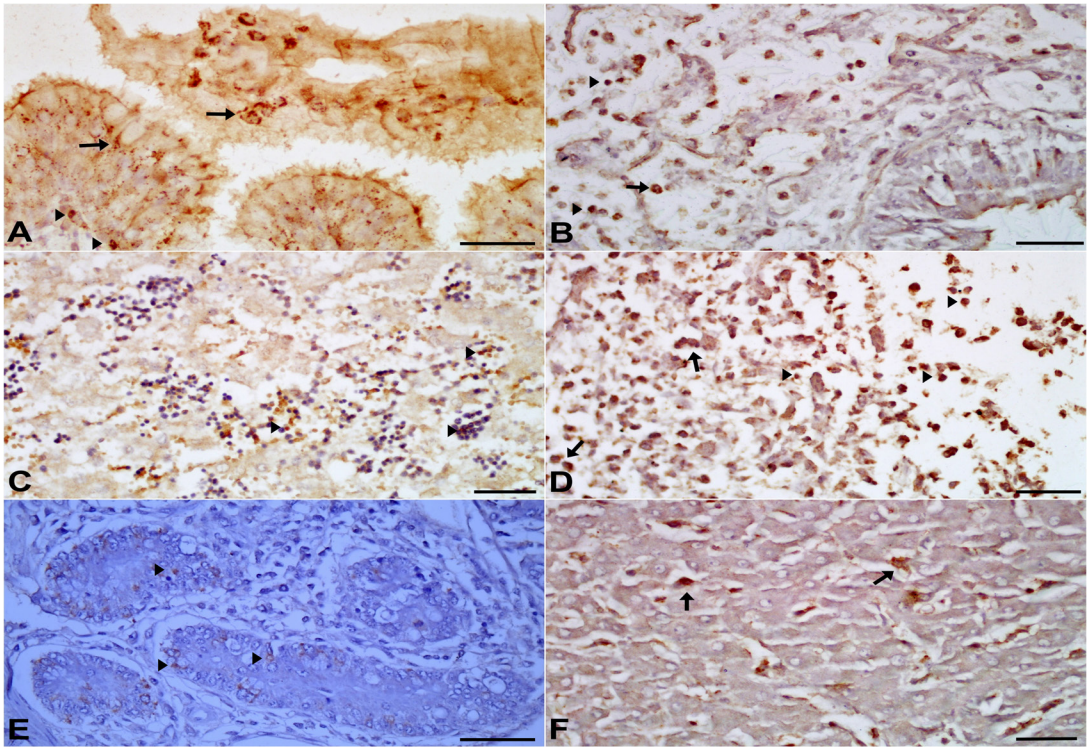

Figure 3. Immunohistochemical staining and positive reactions. A) Lymphocyte (arrowheads), intracytoplasmic staining in bronchial epithelium and lumen (arrows), lung, goat. B) Positive reactions in the cytoplasm of alveolar macrophages (arrow) and lymphocytes (arrowheads) and bronchial epithelium, lung, goat. C) Positive reactions in the cytoplasm of lymphoid cells (arrowheads), spleen, aborted kid. D) Positive reactions in lymphoid cells (arrowheads) and macrophages (arrows), spleen, goat. E) Positive staining in the cytoplasm of crypt epithelium (arrowheads), intestine, goat. F) Positive reactions (arrows) in Kupffer cell cytoplasm, liver, goat. Bar= 50 µm (A-F).

Discussion

Small ruminant lentiviruses are one of the most important viral pathogens affecting sheep and goats worldwide. Both goat and sheep lentiviruses cause chronic inflammatory and degenerative diseases of the brain, lungs, joint tissues, and mammary glands (Blacklaws et al 2004, Ramirez et al 2013, de Miguel et al 2021, Doğan et al 2021). CAEV causes persistent infection, particularly by infecting monocytes and macrophage cells and clinically causes chronic inflammatory disease (Patton et al 2012). SRLVs remain latent in monocytes without producing infectious particles as proviral DNA. The prerequisite for viral replication is the differentiation of monocytes into macrophages, and this differentiation increases markedly under stress, pregnancy, and immunosuppression (Cheblounе et al 1996). This study found that macrophages and mononuclear cell infiltration were predominant in all tissues examined. In previous studies, monocytes/macrophages and dendritic cells were found to be the main target cells of SRLVs. The infected macrophages infiltrating the tissues played a role as Trojan horse in the multisystemic window of infection because they had a large tissue distribution area (Anderson et al 1983, Storset et al 1997, Ryan et al 2000, McNeilly et al 2008, Minguijon et al 2015).

This present study observed histopathologic findings of subacute and chronic pneumonia in all goats' lungs, similar to previous researchers' findings (Turchetti et al 2013, Son et al 2017). Interstitial pneumonia and bronchopneumonia in the lungs, smooth muscle hypertrophy around the bronchi and bronchioles, and intracytoplasmic inclusion in the alveolar epithelium in two of the lung tissue samples, as well as degeneration, necrosis, and desquamation in the bronchiolar epithelium in one goat lung were observed. In addition, positive immunohistochemical staining was detected in the cytoplasm of lymphocytes and macrophages in the bronchial and bronchiolar epithelium, alveolar macrophages, and interalveolar septum. Although arthritis has been reported as the most important clinical finding in CAEV infections in goats older than 1-2 years, in previous studies, interstitial pneumonia is also an important finding (Sims et al 1983, Robinson, Ellis 1984, Dolka et al 2020, Moroz et al 2022). In this disease, an inflammatory reaction consisting of macrophages and lymphocytes in the interstitial tissue of the lung, fibrosis, alveolar proteinosis, thickening of the interalveolar septum, smooth muscle hyperplasia in the bronchioles, and positive immunohistochemical staining of alveolar macrophages and bronchial epithelial cells were noted histopathologically (Patton et al 2012, Eroksuz et al

2022, Moroz et al 2022). ur results support the data on detecting high levels of infected cells and free virions in lung fluid, especially in the late stage of the disease (Blacklaws 2012).

Mononuclear cell infiltrates the interstitial tissue in the kidneys of CAEV-infected animals, inflammation with a predominance of lymphocytes in a large artery at the corticomedullary border, thrombosis in their lumen, and interstitial nephritis in the kidney have been reported (Murphy et al 2021, Eroksuz et al 2022). In the present study, hydropic degeneration and necrosis of the tubular epithelium of the kidneys were observed in half of the goats, and hyaline droplets and hyaline cylinders were observed in two of the kidneys, but no positive reaction was detected immunohistochemically.

Although focal interstitial myocarditis in the heart, thrombotic arteritis in the myocardium, fibrosing myocarditis, and myocardial necrosis to varying degrees have been reported in the infection because of its multisystemic nature (Murphy et al 2021, Eroksuz et al 2022), hyperemia, hyaline degeneration and necrosis were observed in the heart tissue in this study, too but no positive reactions were detected immunohistochemically. However, chronic enteritis with intracytoplasmic inclusions in the crypt epithelium was noted in two of the intestines. Immunohistochemically, positive reactions were noted in macrophages and lymphocytes in the liver and especially in the crypt and villous epithelium, lymphocytes, and macrophages in the intestine. It is suggested that one of the causes of cachexia in animals is these pathologies in the intestinal tissues.

In research, steatosis and multifocal necrosis in hepatocytes and dilatation of the sinusoids have been reported in the liver (Son et al 2017). In present study, liver degeneration and necrosis in the hepatocytes were observed in half of the goats, as well as an increase in Kupffer cells and lymphocyte and macrophage infiltrations. In addition, the spleen, one of the major target organs for SRLV, is also important for the persistence of infection. Immunohistochemically, it has been reported that there are positive responses, mainly in macrophages in the red pulp (Colitti et al 2019). Also, in this study, positive responses were observed in the spleen, especially in lymphocytes and macrophages immunohistochemically, and a decrease in lymphoid cells and an increase in macrophages histopathologically.

Conclusion

In conclusion, this study defined the histopathology of SRLV infection in goat tissues, which has already been detected serologically in Türkiye and occupies an important place in goat breeding. Important information about the pathophysiology of the disease might be obtained by clinical, virological, and histopathological composite studies, which will be planned in the future with more samples.

Conflict of Interest

The authors did not report any conflict of interest or financial support.

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Author Contributions

Motivation/Concept: OK; Design: VSA; Control/Supervision: OK, VSA; Data Collection and/or Processing: VI; Analysis and/or Interpretation: OK, VSA, FD, IES; Literature; Review: OK; Writing the Article: OK, IES; Critical Review: VSA.

Ethical Approval

The study protocol was approved by the Local Animal Ethics Committee of the University of Hatay Mustafa Kemal, Hatay, Türkiye (No. 2021/07-10).