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Features of model coronaviruses distribution in feline organs and tissues in the context of COVID-19 pathogenesis study

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SUMMARY

To date, there is reason to believe that, unlike classical acute respiratory virus infections caused by adenoviruses, rhinoviruses, orthomyxoviruses, COVID-19 behaves completely differently. Firstly, the pathological processes are likely to be immune-mediated and the immune system quite slowly ensures the elimination of the virus from the organism. Secondly, the dynamics of the disease symptom development and the duration of intestinal virus shedding after recovery give reason to believe that the SARS-CoV-2 infection is mainly localized in the intestine. A possible reason is that in the presence of proteolytic enzymes, viral particles mature, hydrophilic amino acids are removed from the surface of the virion, making it more hydrophobic and able to adhere to cells due to hydrophobic interactions. The presence of the ACE2 receptor mainly in the enterocytes of the ileum does not exclude the accumulation of coronavirus in lymphocytes, given that there are more lymphocytes in the gastrointestinal tract than anywhere else, this fact can be considered as another justification for the predominant accumulation of coronaviruses, including SARS-CoV-2 in the intestine. A distinctive feature of feline coronavirus infection and, in particular, infectious feline peritonitis, from human COVID-19 infection was considered to be the presence of effusion peritonitis as the main complication leading to death, while respiratory and cardiovascular insufficiency is more characteristic for humans. Nevertheless, cases of serous peritonitis in humans infected with COVID-19 have already been described. In the context of the analyzed model, the clinical case described in the study allows principal possibility of exacerbation of chronic coronavirus infection in case of re-infection (superinfection) and development of a predominantly local infection.

Keywords: cats, coronavirus, COVID-19, FCoV, SARS-CoV-2, pathoanatomical examination, histological examination

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Изучение особенностей распределения модельных коронавирусов в органах и тканях кошачьих в контексте изучения патогенеза COVID-19

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РЕЗЮМЕ

На сегодняшний день есть основание считать, что в отличие от классических острых респираторных вирусных инфекций, вызываемых аденовирусами, риновирусами, ортомиксовирусами, COVID-19 ведет себя совершенно по-другому. Во-первых, патологические процессы скорее являются иммуноопосредованными, и иммунитет довольно медленно обеспечивает элиминацию вируса из организма. Во-вторых, динамика развития симптомов заболевания, длительность вирусовыделения из кишечника после переболевания дают основание считать, что SARS-CoV-2 находится преимущественно в кишечнике. Возможной причиной этого является то, что в присутствии протеолитических ферментов происходит созревание вирусных частиц, удаление гидрофильных аминокислот с поверхности вириона делает его более гидрофобным и способным прилипать к клеткам за счет гидрофобных взаимодействий.

Наличие рецептора ACE2 главным образом в энтероцитах подвздошной кишки не исключает накопление коронавируса в лимфоцитах. Учитывая, что лимфоцитов в желудочно-кишечном тракте больше, чем где-либо, этот факт можно рассматривать как еще одно обоснование преимущественного накопления коронавирусов, в т. ч. SARS-CoV-2, в кишечнике. Отличительной чертой коронавирусной инфекции кошек, и в частности инфекционного перитонита кошек, от COVID-19 человека считалось наличие выпотного перитонита в качестве основного осложнения, ведущего к смерти, в то время как для людей более характерна дыхательная и сердечно-сосудистая недостаточность. Тем не менее уже описаны случаи развития серозного перитонита у людей на фоне COVID-19. В контексте анализируемой модели описанный в работе клинический случай допускает принципиальную возможность обострения хронической коронавирусной инфекции при повторном заражении (суперинфекции) с развитием преимущественно локальной инфекции.

Ключевые слова: кошки, коронавирус, COVID-19, FCoV, SARS-CoV-2, патолого-анатомическое исследование, гистологическое исследование

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INTRODUCTION

The global coronavirus pandemic has changed life and affected not only human but animal health as well. The circulation of SARS-CoV-2 was most often detected in domestic cat population. It should be noted that among pets with confirmed laboratory diagnosis there were animals that had contacts with SARS-CoV-2-infected owners and sheltered (stray) animals [1].

Two serotypes (I and II) of feline coronaviruses (FCoVs) are circulating in feline population. Each serotype is represented by two biotypes with different pathogenicity: feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV) [2]. The leading theory of feline infectious peritonitis (FIP) development is based on the assumption that FIPV emerges as a result of somatic mutations in the *de novo* FECV genome, leading to changes in the FECV tropism for enterocytes to tropism for monocytes and macrophages. The more pathogenic FIPV replicates in macrophages [3].

Infectious peritonitis causes animal mortality in 100% cases and is accompanied with liver dysfunction, often pulmonary edema and damage to the central nervous system [4]. Although the prevalence of FCoV infection in feline population is high, the FIP infection rate is quite low and rarely exceeds 5% of FCoV-infected cats raised in multiple-cat households [5].

The FCoV genome is represented by a single-stranded RNA encoding four structural proteins (the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins) and seven non-structural proteins [6]. The FCoV spike (S) protein is considered the viral regulator of binding and entry to the cell, and it is also involved in FCoV tropism and virulence. Mutations in the S protein coding sequence of FCoVs appear to be responsible for the change in viral tropism from enterocytes to monocytes and macrophages. As a result, FCoV enters the bloodstream and causes peritonitis [7].

There are similarities between FCoV and SARS-CoV-2:

1. Not all cats exposed to FCoV become infected, not all infected cats remain FCoV carriers for a long time, only a few cats infected with FCoV die from infectious peritonitis.

2. Severe damage to the respiratory system in humans with COVID-19, as well as multiple organ failure in cats with FIP, are associated with the immune system response when immunocompetent cells damage organs and tissues [8].

The data published by a group of Chinese researchers show that cats are able to develop an immune response to SARS-CoV-2 [9]. Moreover, SARS-CoV-2 can be transmitted from cat to cat [10]. The question of whether this is followed by the development of an infectious process in a cat or whether it leads to a change in the course of an already existing coronavirus infection remains open. Besides, it is not clear, whether cats play a role in the spread of SARS-CoV-2 among humans, whether humans are able to develop an immunological response to FCoV and, if possible, whether it affects the course of COVID-19-associated infection?

The dry form of infectious feline peritonitis appears to be most similar to the acute form of COVID-19 in humans [11]. Similarities include vasculitis, the immune-mediated nature of organ and tissue damage (including antibody-dependent infection enhancement, ADE), dissemination of the pathogen from the gastrointestinal tract [12].

The aim of the paper is to study the distribution of model coronaviruses in feline organs and tissues in the context of COVID-19 pathogenesis study.

MATERIALS AND METHODS

The concept of the pathogenesis of combined coronavirus superinfection in humans was considered based on the example of studying the pathogenetic mechanisms of both SARS-CoV-2 and FCoV infections in cats.

The research was conducted in the animal facility of the SFSCA RAS. The study was aimed at the cats that died from various forms of infectious peritonitis after contact with infected owners, as well as at the cats that were PCR-positive for FCoV and SARS-CoV-2 genome RNA. The qDNA and samples of formaline-fixed feline and human biomaterial were tested using reverse transcription polymerase chain reaction (RT-PCR) and immunofluorescence microscopy.

The study of the FCoV distribution in FIP-affected animals was carried out using the real-time RT-PCR. RNA was isolated from internal organs using phenol-chloroform extraction method, a cloned fragment of a targeted gene was used as a control. Quantification of the control DNA was carried out using FCoV-specific digital PCR. For control of RNA expression and normalization, the bacteriophage MS2 RNA (an external control sample that was added to each reaction) and the mRNA of feline housekeeping genes (GAPDH) were evaluated.

The pathology specimens were fixed in 10% buffered formalin. After histological treatment, the paraffin sections were dewaxed in xylene, then the xylene was removed with ethanol and the sections were immersed in 100 mM Tris-HCl solution. Antigens were unmasked by heating in a microwave oven in a citrate buffer solution (pH 6.0).

The cell nuclei were stained with Hoechst 33258 (Invitrogen, USA), the S-protein fragment was detected using rabbit polyclonal antibodies SARS Coronavirus Spike Protein Antibody Cat. No. PA1-41375 (Invitrogen, USA). The reaction was carried out in 0.05 M phosphate buffered saline (pH 7.2) with the addition of 0.02% Tween-20 (PBS-T) and 0.3% bovine serum albumin. Donkey Anti-Rabbit IgG (H+L), Mouse/Rat/Human SP ads-AF555, Cat. No. 6440-32 (SouthernBiotech, USA) were used as a conjugate in the same buffer solution. The reaction was carried out at room temperature for an hour. The unbound PBS-T antibodies (pH 7.2) were washed with distilled water, enclosed in glycerin and subjected to microscopy using an Imager D1 fluorescent microscope (Zeiss, Germany) and AxioVision software. Luminescence was detected using light filter systems FS 49, FS 10, FS 20. Similar histological products containing no primary antibodies were used for control of nonspecific binding of the conjugate.

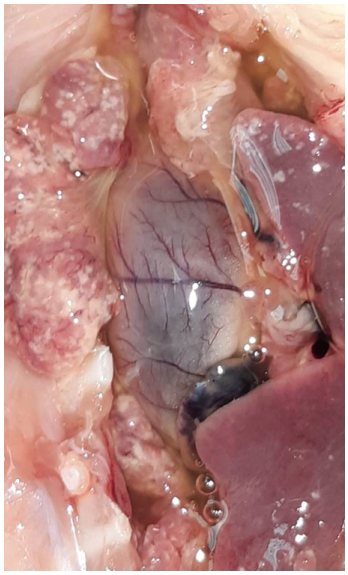

Fig. 1. Lesions in the thymus, pulmonary edema, hydrothorax

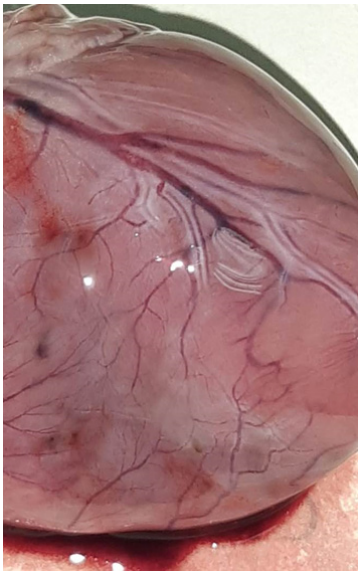

Fig. 2. Right-sided myocarditis, myogenic dilatation and hemorrhages with areas of focal hyperemia and ischemia

RESULTS AND DISCUSSION

Study of the FCoV distribution in organs and tissues of a kitten with a dry form of FIP (clinical case). Case history: all kittens from the same litter at the age of two months got diseased showing signs of rhinorrhea, diarrhea and depression. One of the kittens began to lose weight at the age of five months and was euthanized with a diagnosis of a dry form of FIP. The diagnosis was based on the detection of genomic RNA of FCoV in a pleural transudate. Also, at the time of diagnosis establishment, the concentration of urea in sera decreased to 3.5 mmol/L, the level of triglycerides increased to 95 g/L, globulins – up to 70 g/L, the ratio of albumin/globulin was 0.4. Other biochemical parameters (glucose, creatinine, albumin, alanine aminotransferase, alkaline phosphatase) were within normal limits. Neutrophils, single macrophages and lymphocytes were identified in a pleural smear. Hematocrit was lowered to 21.6%, hemoglobin was 9% below normal, eosinophils were 90% below normal, platelet count – 2% lower (171 cells/μL). The other hematological parameters were within the normal range. Tomography showed a large amount of fluid in the thoracic cavity, areas of higher-density infiltration, increased X-ray density in cranial lobes of the lungs with areas of consolidation. Pulmonary interstitial density was observed mainly in the area of the cranial lobe of the left lung, bronchiectases were also noted.

The animal carcass was subjected to necropsy immediately after euthanasia. The following organs were collected for testing: the brain (pituitary gland, frontal lobe of the cerebral cortex, corpus callosum, olfactory bulb, parietal region of the brain, cerebellum, dura mater), lymph nodes (mesenteric, pharyngeal, mediastinal, axillary, submandibular), blood samples (from the portal vein, left and right heart ventricles), lung, choanae, larynx, trachea, thoracic transudate, organs of the gastrointestinal tract (duodenum, colon, liver), thymus, spleen, parotid salivary gland.

Analysis of pathophysiological and pathologic-anatomical mechanisms of organ system damage in cats with FIP in combination with SARS-CoV-2 infection. Pulmonary edema, inflammatory changes in the thymus, hyperplasia of mediastinal lymph nodes, accumulation of fluid in the thoracic cavity were observed during the necropsy. Noteworthy is also myogenic dilatation and hemorrhages in the myocardium of the right heart ventricle (Fig. 1, 2). The trachea and bronchi had no changes, but the choanae were hyperemic.

Necropsy of abdominal organs showed inflammatory changes mainly in the mesenteric lymph nodes (Fig. 3). No inflammatory changes in the gastrointestinal mucosa or signs of pyogranulomatous polyserasitis were detected. No fluid was present in the abdomen. The spleen was also uneven in colour, splenitis manifestations were observed.

Assessment of FCoV distribution in a kitten. Anatomical mapping of the FCoV distribution made it possible

to detect viral RNA in the intestinum colon, blood of the right and left heart ventricles, mediastinal lymph node, portal vein, thoracic transudate, thymus and lung.

The virus was not detected in other parts of the gastrointestinal tract and lymph nodes, choanae, brain, liver and kidneys, or its concentration was below the detection threshold.

The largest amount of FCoV was found in the colon, the viral load was 3.02 times less in the lung, and the concentration of the pathogen was 1.46 times less in the thymus than in the lung. The amount of the viral RNA was 2.8 times larger in the blood of the left heart ventricle than the right one, and 5.7 times less in the portal vein than in the blood of the right ventricle (Fig. 4).

Correlation of the distribution of the SARS-CoV-2 antigen in human lungs and internal organs of a cat with combination of COVID-19 and FIP infection. As the study results by some authors have shown, from the histological picture observed when the human lungs are affected by the SARS-CoV-2 virus, it follows that the viral antigen (a fragment of S-protein between the sites of proteolytic cleavage by furin and TMPRSS2), in addition to the affected cells of the respiratory epithelium and macrophages, is detected on erythrocytes [13]. A fragment of a coronavirus spike protein is not necessarily associated with viral particles. Nevertheless, in the context of immune-mediated lung damage, the presence of this antigen may have pathogenetic significance.

It is an interesting fact that not all red blood cells in the lung tissue are stained with antibodies to SARS-CoV-2 (they are intensely black under luminescent microscopy) [14]. Also, the immune staining reaction was absent in preparations containing no primary antibodies, which reduces the likelihood of an artifact (but does not definitively exclude it).

The SARS-CoV-2 S-protein antigen is also visualized in the lungs of a cat that is PCR-positive for the presence of SARS-CoV-2 genomic RNA (Fig. 5), however, it is observed mainly on the apical surface of the cells of the respiratory epithelium, but not within the interstitium or blood vessels. Thickening of the interalveolar septa and signs of karyolysis, including in the absence of localization of this antigen, do not allow us to assume a topological relationship between the localization of the antigen and the pathological process (see also RT-PCR results for FCoV, shown in Figure 4).

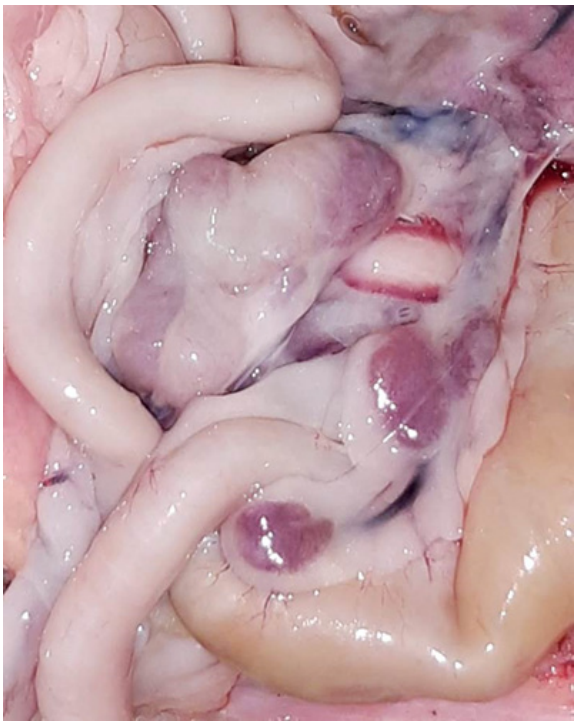

Fig. 3. Inflammation of mesenteric lymph nodes

Despite the fact that based on PCR data there are quite large amounts of FCoV in the intestine, the SARS-CoV-2-related virus was not detected in the intestine either using PCR or immunofluorescence technique (Fig. 6). The absence of a signal also makes it possible to exclude non-specific binding of fluorescently labeled antibodies to erythrocytes.

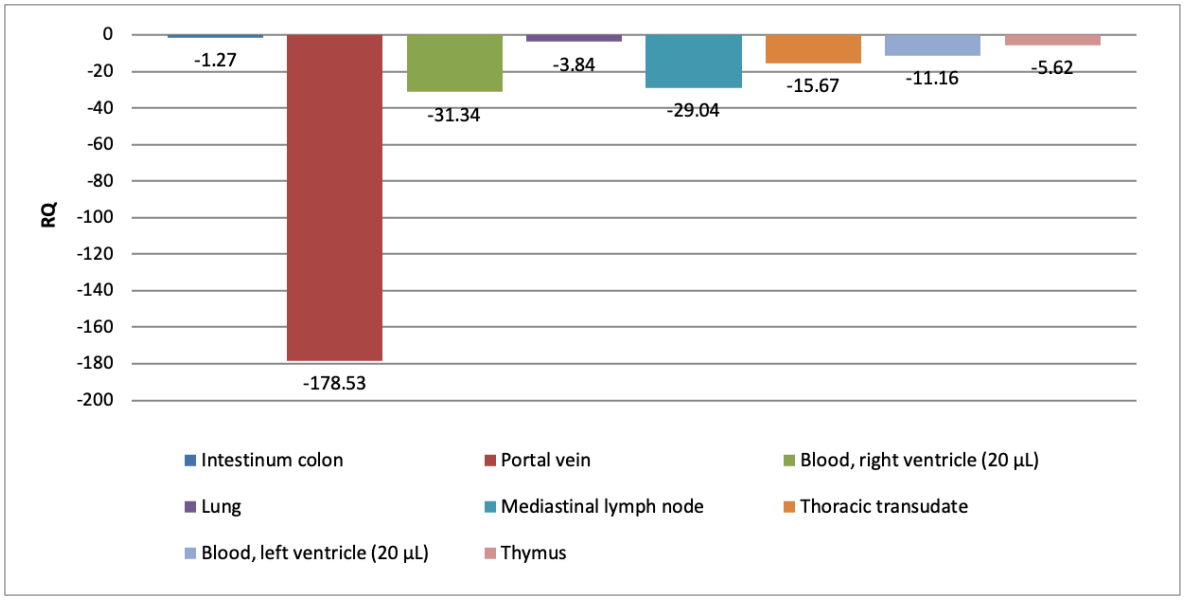

Fig. 4. Relative quantity of FCoV genomic RNA (ddCt) in different organs of a kitten

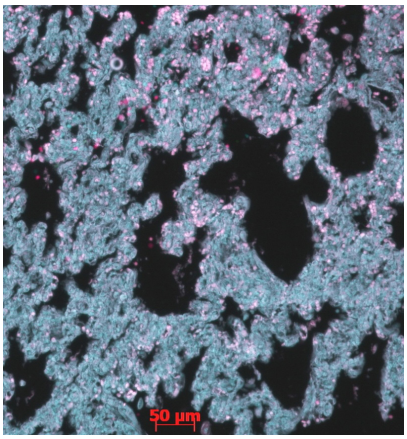

Fig. 5. SARS-CoV-2 antigen distribution in feline lung tissue (immunofluorescence, Hoechst 33258 staining of anti-SARS-CoV-2 S-protein antibody and AlexaFluor 555-labeled conjugate, 150× magnification)

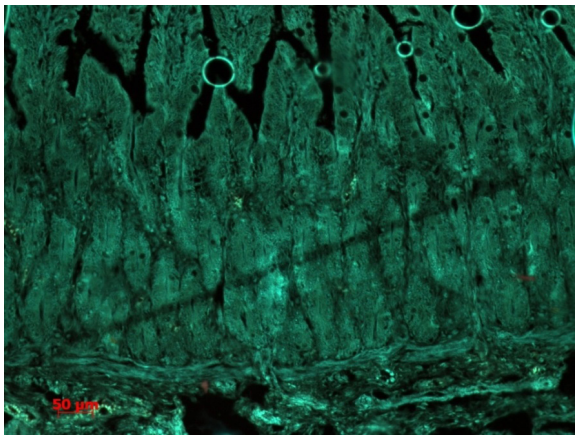

Fig. 6. Distribution of SARS-CoV-2 antigen in feline jejunal tissue (immunofluorescence, Hoechst 33258 staining of anti-SARS-CoV-2 S protein antibody and AlexaFluor 555-labeled conjugate, 150× magnification)

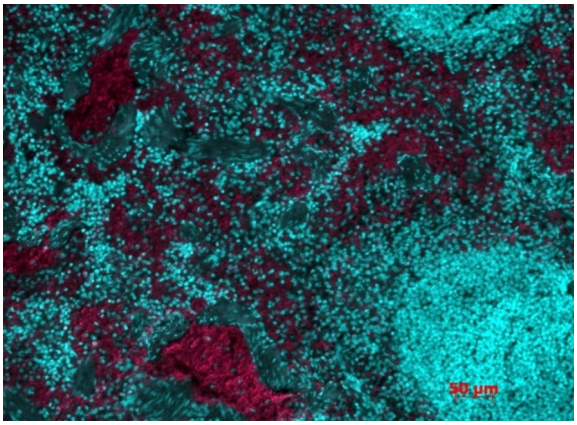

Fig. 7. Distribution of SARS-CoV-2 antigen in feline spleen (immunofluorescence, Hoechst 33258 staining of anti-SARS-CoV-2 S protein antibody and AlexaFluor 555-labeled conjugate, 150× magnification)

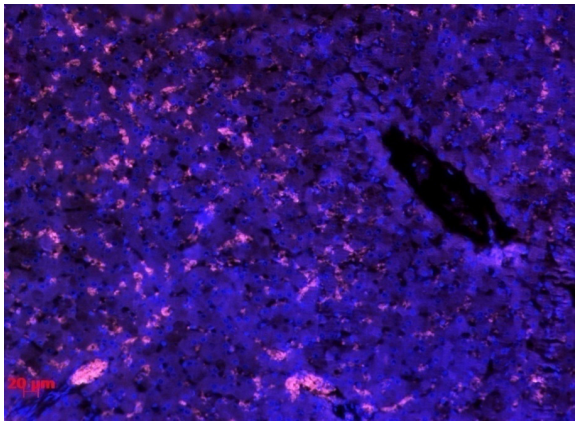

Fig. 8. Distribution of SARS-CoV-2 antigen in liver (immunofluorescence, Hoechst 33258 staining of anti-SARS-CoV-2 S protein antibody and AlexaFluor 555-labeled conjugate, 150× magnification)

The largest amount of SARS-CoV-2 S-antigen is observed in the spleen, but mainly in the composition of red blood cells in the lumen of blood vessels, red pulp and macrophages. No antigen was detected in the lymphoid nodules of the spleen (Fig. 7).

The data of immunofluorescence analysis of the liver present the greatest interest. The SARS-CoV-2 S-protein antigen is distributed in capillaries mainly located perilobularly (Fig. 8). It is also found in the lumen of the hepatic arteries, but not in the branches of the portal vein. These data are consistent with the results of the detection of the analyzed virus protein in the lungs, but not in the intestine. The uneven microcirculation of blood from the hepatic artery and portal vein suggests the formation of centrilobular hypoxia due to immune-mediated aggregation of erythrocytes (entering the liver from the lungs) or vasoconstriction caused by the interaction of S-protein with ACE2 receptors of blood vessels.

Analysis of the distribution of viral RNA in blood vessels allows us to speculate about the possibility of both hematogenic and lymphogenic transport of coronaviruses from the intestine to the small pulmonary circulation (Fig. 4). The unequal amount of viral RNA in the portal vein, liver and right heart ventricle gives only two possibilities for a sharp increase in the concentration of the virus in the right ventricle: 1) a large amount of viral particles can form in the liver (despite the fact that viral RNA was not detected by RT-PCR), 2) a significant part of the viral particles enters the lymphogenic pathways either from the intestine or from mesenteric lymph nodes (however, viral RNA was not detected by PCR). The uneven nature of inflammatory processes in mesenteric lymph nodes should be noted.

The asymmetric myocardial injury (right-sided myocarditis and myogenic dilatation, Fig. 2) suggests a longer-term entry of the viral agent to the lungs from the large circulatory circle, and not from the upper respiratory tract, where the virus is not detected. Despite the lung injury due to coronavirus causing a condition incompatible with life, RT-PCR proved to be an insufficiently sensitive method for detecting the virus in the nose. This fact makes it possible to doubt the high efficacy of PCR diagnosis of coronavirus pneumonia, including in humans, when trying to detect the virus in the nasal passages or oral cavity.

Various forecasts can be made based on the above assumptions. The virus has to shed in the intestine for

a long time (and this forecast has been realized), including in humans with antibodies. The incubation period for this type of virus reproduction and distribution can be quite long and/or accompanied with asymptomatic carrying (it would be difficult to imagine a long-term asymptomatic virus carrying in the bronchi and trachea).

This hypothesis also explains that intestinal lesions are recognized as the earliest COVID-19 manifestations. A sharp increase in the virus concentration in the lungs may occur when the virus is identified in the intestine by immune cells, intestinal inflammation develops, intestinal perfusion increases and, accordingly, the viruses, activated T cells and neutrophils massively enter the right atrium and ventricle through the caudal vena cava (which should mainly cause right-sided heart damage).

In order for the SARS-CoV-2 RNA to get packaged into the capsid of another virus, it should specifically bind to the N nucleocapsid protein. M protein is likely to participate in this process [15]. That is, this process cannot occur with all types of coronaviruses. However, it seems possible to compare the RNA secondary structures of different coronaviruses and N amino acid sequences (preferably, tertiary structures) and predict the risks of spillover between different species using bioinformatics methods. If we take into account the similarity of FCoV and SARS-CoV-2, the formation of a viral RNA complex of *Betacoronavirus* genus representatives with the nucleocapsid protein of the genome of the infectious bronchitis virus (IBV) is unlikely.

CONCLUSION

The results obtained in the study helped to specify some epizootological characteristics of the disease, confirm and supplement the available clinical data on animals infected with FCoV and SARS-CoV-2, as well as facilitated the study of pathologic and anatomical picture and histological changes typical of this pathology.

The study provided evidence for the mechanisms of coronavirus distribution and spread from the organs where the greatest replication of the virus occurs (thymus and intestines) to the lungs, where there is an accumulation of viral particles trapped by the hematogenic pathway in a smaller volume relative to other target organs. Intestinal lesions are considered among the COVID-19 earliest manifestations [16]. A sharp increase in the virus concentration in the lungs may occur when the virus is identified in the intestine by immune cells, intestinal inflammation develops, intestinal perfusion increases and, accordingly, viruses, activated T cells and neutrophils massively enter the right atrium and ventricle through the caudal vena cava (which should mainly cause right-sided heart damage).

In the context of the analyzed model, the clinical case described in the study allows principal possibility of exacerbation of chronic coronavirus infection in case of re-infection (superinfection) and development of a predominantly local infection. The presented data also shed a new light on red blood cells. The unevenness of the erythrocyte population in relation to the presence of the S-protein antigen gives reason to consider them as false targets when interacting with the virus or as carriers of adsorbed virus antigens. The revealed facts require further studies.

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