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Respiratory form of infectious rhinotracheitis: Analysis of immunomorphological reactions

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Abstract. The concentration of cattle in limited areas, nutritional disorders, and imbalance of micro- and macroelements contribute to suppression of natural resistance of the organism, insufficient live weight gain, leading to the growth of infectious diseases of young animals with high rates of forced slaughter and cattle mortality. The source of the causative agent of rhinotracheitis infection – *Bovine alphaherpesvirus 1* hinders the development of the livestock industry, thus, it is necessary to search for possible approaches to prevent and control this infection. The purpose of the research

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is to determine the immunomorphological changes in the lymphoid tissue of the trachea and bronchial system, in the regional lymph nodes of the lungs and in the spleen in calves naturally affected by infectious rhinotracheitis. The experimental studies were based on the research of immunomorphological reactions in lymphoid tissue during infection of young cattle with *Bovine alphaherpesvirus 1*, using polymerase chain reaction, histological and immunohistochemical methods. According to the results, it was established that hyperplasia of trachea-associated lymphoid tissue was observed in the trachea, and hyperplasia of bronchial-associated lymphoid tissue was observed in the lungs; the affected areas of the trachea and lungs were infiltrated with lymphocytes, macrophages and plasma cells. The immunomorphological reactions of regional lymph nodes demonstrate hyperplasia of B- and T-dependent zones, and in the spleen – hyperplasia of T-dependent zones of the white pulp. Thus, immunocompetent cells of lymphoid tissue associated with B- and T-dependent areas of the trachea, bronchial system of the lungs and regional lymph nodes of the lungs, and with T-dependent areas of the spleen, are directly involved in the pathogenesis of infectious rhinotracheitis of respiratory type calves. Antibacterial therapy with antibiotics destroys pathogenic and normal flora in the intestine, but they are not effective enough on viral infection, therefore, production trials of effective means of specific prophylaxis and vaccination are the primary task of veterinary medicine

Keywords: cattle; herpesvirus; polymerase chain reaction; pathology; immunomorphology; associative diseases

INTRODUCTION

Diseases of young animals caused by viruses occupy an important place in the structure of diseases of cattle. The etiological structure of infections of calves is represented by: infectious rhinotracheitis, viral diarrhoea, parainfluenza, respiratory syncytial virus, rotavirus, and coronavirus – the causative agents of all these infections are opportunistic viral flora that activate when natural resistance of the organism is suppressed. As noted by M.J. Counotte *et al.* (2016), the above infections lead to significant economic losses, including treatment costs, ineffective prevention, reduced productivity of sick calves and their death. They account for 34.1-47% of all diseases under conventional livestock production methods, and more than 60% of all diseases in young cattle under industrial methods.

According to C. Iscaro *et al.* (2021), these diseases affect 82-100% of calves under one year of age, some of them recurrent – 9.6-17.2%. The causative agent of rhinotracheitis is the genomic virus BHV-1 (*Bovine Herpesvirus 1*), which is resistant to low temperatures, unstable to the external environment and sensitive to various chemicals: 2% formalin solution, 1-2% hot alkali solution, 10-20% quicklime solution, 0.3% estosteril-1 solution. Exposure to sunlight for 48 hours kills the virus.

Herpesvirus diseases of cattle are widespread, with bovine herpesvirus infection type 1, or Infectious Bovine Rhinotracheitis IBR-1 (IBR-1), being the primary cause. K.J. Mars *et al.* (2019) reported that economic losses from respiratory diseases of young cattle in countries with well-developed commercial livestock production are enormous, with mortality rates of 5-20% and sometimes as high as 60%. As noted in the work of Zh. Atambekova *et al.* (2023), reproduction of herpesviruses in susceptible cells is a complex process involving many virions, cells, virus-inducing and virus-modifying enzymes subdivided into stages of development of herpetic infection: primary infection of the skin and mucous membranes; "colony-formation" and acute ganglion infection; latent infection with the herpes virus. In addition to rhinopharyngitis, associated infectious diseases of cattle are: viral diarrhoea, mucous membrane disease, parainfluenza type 3, respiratory syncytial virus and adenovirus infections, mycoplasmosis, chlamydia, pseudomoniasis, trichomoniasis and trichinellosis.

J.J. Hodnik *et al.* (2021) estimate that clinical syndromes in the feedlot are frequently associated with respiratory infections. Disease in cattle on IBR-1 should be prevented before it occurs and becomes latent in animals that have recovered from primary infection, as any type of stress that increases endogenous cortisol levels, including administration of exogenous corticosteroids, can lead to virus recurrence. K. Kydyshov *et al.* (2022) state that during virus reactivation, infected cattle excrete IBR-1 virus through the eyes, nose and genital secretions. Close contact between large numbers of cattle establishes ideal conditions for the rapid spread of IBR-1 virus. Serum-neutralising antibodies prevent infection but do not eliminate degradation or release of latent BHV-1 virus.

The purpose of this research is to explore the morphological and cellular composition and to determine the immunomorphological changes in lymphoid tissues associated with the trachea and bronchial system of the lung, and in pulmonary lymph nodes and spleen in calves.

THEORETICAL OVERVIEW

IBR-1 infection of cattle is a viral infection occurring predominantly in the respiratory and urogenital systems, characterised by elevated body temperature, scarring and necrotic inflammation of the mucous membranes of the upper respiratory tract, eyes, genitals, central nervous system and abortive lesions. The causative agent of IBR-1 infection in cattle is herpesvirus

BHV-1, family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genus *Varicellovirus*.

World Organisation for Animal Health (WOAH) (2017) classified herpesviruses according to the cell types involved in the infectious process, their persistence in the natural host and their pathogenicity against phylogenetically similar organisms. They classified them into three groups according to differences in virulence to phylogenetically similar organisms. According to the data, the virus is considered to be classified into strains: type 1 IBR, type 2 (subtypes 2a and 2b) and type 3 (subtypes 3a and 3b). BHV-1 is associated with the major clinical syndromes, Infectious Pustular Vulvovaginitis (IPV) and Infectious Pustular Balanoposthitis (IPB).

According to the research data of J. Wang *et al.* (2007), BHV-1 has a size of 150-200 nm and is a cubic symmetric phage containing 162 phages. The sedimentation constant of the mature virus is 1630-1830 S. BHV-1 is viable for 7-9 minutes at 60-70°C, inactivated within 20 minutes at 56°C, 4-10 days at 37°C, 50 days at 22°C. BHV-1 is sensitive to acetone, ether, and chloroform, e.g., a 1:500 formalin solution inactivates the virus in 24 hours, and a 1:4000 formalin solution inactivates the virus in 46 hours. As reported by S. Nandi *et al.* (2009), when infecting cattle, the virus persists in the organism for 6-12 months and poses a threat to healthy animals in the herd, and IBR-1 virus is cultured in calf kidney cells and cattle embryos.

C. Righi *et al.* (2023) reported that the incubation period of BHV-1 is 2-21 days, but the clinical picture depends on the type and course of the disease, manifested by upper respiratory tract lesions, vaginitis, encephalitis, conjunctivitis and arthritis to varying degrees. In addition, cattle of any gender and age are susceptible to BHV-1, but the disease is most severe in young beef cattle. As established by G. Duca *et al.* (2022), genital infections in female heifers and heifers are characterised by purulent vulvovaginitis, ovariitis, orchitis and salivary gland infection, with pustules and vesicles developing on the genitals and penis of affected bulls. According to J.V. Rosete Fernández *et al.* (2023), in lactating cows, BHV-1 viruses can cause intrauterine foetal death, abortion late in pregnancy and death of non-viable calves a few days after birth, and there are known cases of acute mastitis in cows resulting in reduced milk production.

As reported by P. Mottaghian *et al.* (2022), keratoconjunctivitis caused by BHV-1 can be either independent or concomitant with other diseases. In this disease, the mucous membranes of the conjunctiva, cornea and third eyelid become inflamed, resulting in lacrimation, increased sensitivity to light and mucosal oedema. The cornea often loses transparency and becomes cloudy, and a warty cortex appears. According to C.A. Evans *et al.* (2021), typical neurological signs in young animals are acute agitation, aggression and impaired motor coordination. In contrast, severe depression is observed in some animals. The disease is accompanied by muscle tremors, convulsions, salivation and paralyses, ending in death. Cutaneous aetiology of BHV-1 is observed mainly in bulls and is characterised by skin lesions of the anus, spine, perineum, buttocks and scrotum, accompanied by hair loss and eczema-like rash, and lesions are accompanied by genital lesions anal crepitus or orchitis, as noted by A. Martucciello *et al.* (2023).

Assessment of the general pathogenesis is associated with clinical and morphological manifestations of various respiratory lesions of viral aetiology in cattle, and in many cases these diseases are interrelated, complicating accurate diagnosis and the development of therapeutic and preventive methods for the treatment of IBR-1. According to S.R. Compton (2020), pathological autopsies, virological studies, histopathological studies, histopathological studies using polymerase chain reaction (PCR), and immunohistochemical studies are currently being performed to fully diagnose BHV-1 to explore its pathogenesis and immunogenesis. To enhance epidemiological surveillance of infectious diseases, a multidimensional Syndromic Surveillance (SyS) system is gaining popularity, allowing simultaneous evaluation and synthesis of information from different data sources, as planned in the work of C. Faverjon *et al.* (2019).

In a work by E.R. Snyder *et al.* (2019), reported that the presence of infection is only indicated by analysing viral DNA in the nucleus of nerve cells. The BHV-1 viral genome consists of double-stranded DNA with a virion diameter of 120-140 nm, which encodes about 70 proteins, among which 33 structural and more than 15 non-structural proteins were identified. Nine structural proteins have been identified in the viral DNA (VP105, VP90, VP74, VP64, VP54, VP50, VP47, VP40, and VP31), but the proteins VP74 and VP90 involved in A-gene conversion have the greatest immunogenicity.

As reported by T.G. McDaneld *et al.* (2022), molecular diagnostic techniques have the advantage of high throughput of analysis and rapid results, allowing scientists to amplify a very small DNA sample sufficiently for detailed research. The PCR, histological and immunohistochemical data obtained from the liver demonstrate that the liver is a key organ for etiological diagnosis and that viral glycoproteins, which are located in the envelope on the surface of the virion, play an important role.

MATERIALS AND METHODS

The experimental study was based on histological and immunohistochemical methods of analysis of immunomorphological reactions in lymphoid tissues during infection of young cattle with BHV-1 virus. The methods of analysis and synthesis, diagnostics, analogy, and systematisation were used as a methodological foundation. The objects of the research were tissue samples of trachea, bronchi, lung lymph nodes and spleen.

The incidence of IBR-1 has a seasonal character, due to sharply increasing resistance in the winter months. Experimental trials were conducted in the cold period – from October to December 2022, on cattle in farms of Chui oblast, Kyrgyzstan. Histological and immunohistochemical studies were conducted at the Department of Veterinary and Sanitary Expertise, Histology and Pathology, Kyrgyz National Agrarian University named after K.I. Skryabin.

Lymphoid tissue is represented by lymphoid follicles, therefore, to determine the initiation of immune response to airborne pathogens and antigens, it is necessary to perform a morphological evaluation of lymphoid tissue associated with the trachea, bronchi, regional lymph nodes of the lungs and spleen of young cattle killed by IBR-1. Following the method of analogy, two groups, control and experimental, 3 heads in each, aged 4-5 months, were developed and subjected to pathological autopsy. Histological preparations of the trachea, lungs, lung lymph nodes and spleen of the control group were taken from clinically healthy calves. Samples of pathological material of the experimental group from infected animals were taken during the period of maximum manifestation of clinical signs (temperature reaction, oppression, inflammatory processes in the upper respiratory tract, serous discharge from the nasal cavity and eyes). Laboratory tests of blood serum from 10 heads of diseased calves for the presence of antibodies to the BHV-1 virus by PCR method were performed.

Tissue samples were stabilised no later than 2 hours after slaughter. Tissue samples of the trachea, lungs, lymph nodes and spleen were prepared in the laboratory according to the generally accepted methods of the European Food Safety Authority (EFSA) (Istituto Superiore di Sanità, 2021) and fixed in 10% neutral formalin solution for histological and immunohistochemical studies. Paraffin blocks were developed, from which thin histosections 3-5 μm in diameter were prepared. Hematoxylin-eosin and Van-Gizon methods were used for staining tissue samples.

The animals were kept, cared for and fed according to the provisions and diets recommended for this type of animals. The peroxidase-anti peroxidase (PAP) method and anti-PCNA (proliferating cell nuclear antigen) monoclonal antibody, Clone PC10, were used for immunohistochemical studies. Histological preparations were examined using a LEICA ICC 50 HD binocular microscope at magnifications of 50, 100 and 200. Microphotography was performed using the digital camera of this microscope. All experimental studies were carried out in accordance with modern methodological approaches and in compliance with relevant requirements and standards, in particular, the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986).

RESULTS

The assessment of tissue damage from IBR-1 disease is based on pathological and anatomical changes and clinical examination. This work describes the morphofunctional state of immunogenic peripheral organs – lymphoid tissue associated with the trachea, lungs, regional lymph nodes and spleen. Autopsy of young cattle with severe IBR-1 acute respiratory inflammation usually demonstrates serous conjunctivitis, catarrhal pyogenic rhinitis, laryngitis, tracheitis and mucosal lesions of the appendicular cavities.

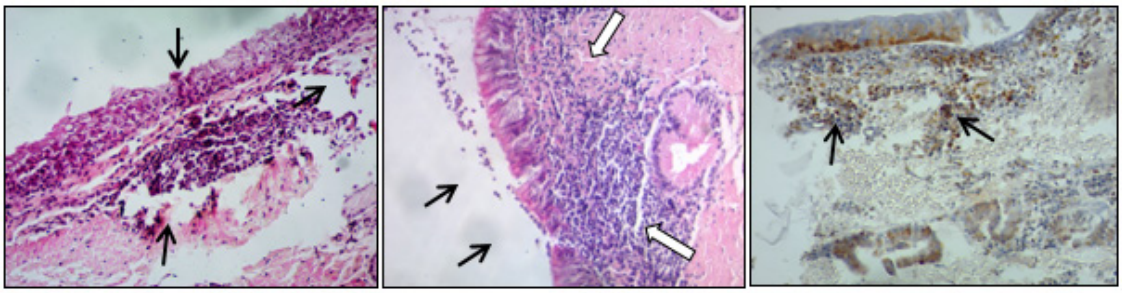
The clinical picture of the condition of experimental animals was marked by swelling, hyperaemic mucosa of the nasal cavity covered with mucopurulent plaque, erosive lesions of various shapes and sizes, purulent exudates accumulating in the nasal cavity and appendicular cavities, on the mucous membranes of the larynx and trachea. Severe forms of IBR-1 rhinotracheitis contribute to pathohistological changes in regional bronchial and mediastinal lymph nodes and the spleen. Therefore, acute serous or serous-necrotising lymphadenitis and follicular hyperplasia are noted in calves. In the acute form of IBR-1 in calves, the tracheal mucosa is locally necrotised, and the lumen of alveoli and bronchioles in the affected area is filled with serous exudate, the interstitial tissue is markedly oedematous, there is hyperaemia and haemorrhages on the skin of the nasolabial mirror. When the eyes are affected, the conjunctiva becomes hyperaemic with oedema spreading to the conjunctiva of the eyeball, which may be covered with plaques established by papillary nodules, small erosions and ulcers up to 2 mm in size. Usually, on days 3-5, a dry cough appears, which later changes to a moist cough with serous purulent discharge from the eyes and nasal passages. Breathing becomes more frequent, heavy, predominantly abdominal type, accompanied by wheezing. Sick animals are lethargic, inactive and mostly lying down. Feed refusal and cachexia are noted.

The lymph nodes of calves with respiratory IBR-1 demonstrate serous or serous-necrotising lymphadenitis, follicular hyperplasia and, as the disease progresses, lymph node atrophy, a decrease in the number of lymphoid follicles and thinning of the paracortical zone. EFSA AHAW Panel *et al.* (2017a) identified that IBR-1 in the spleen of severely affected calves demonstrated necrotic lymphocytes and small cell foci with infiltration, with 12 cases presenting 52.2% necrosis and devastation of lymphoid tissue. The asymptomatic form of viral herpetic infection of cattle is due to the prolonged persistence of BHV-1 virus in the animal and manifests itself in three main forms: latent, chronic, and slow viral infection. J.H. Hernandez-Medrano *et al.* (2021) reported that when the body is infected with the virus, specific humoral and cellular immunity factors including antibodies, macrophages, lymphocytes, and leukocytes exert a protective effect. The latent nature of BHV-1

in individual animals depends on the Immunofluorescence Assay (IFA) antibody assay, but the PCR test determines the presence of the virus even at an early stage of the disease with high sensitivity.

IBR-1 infection can be presumed based on clinical, pathological and epidemiological findings, but laboratory serological or virological investigations are required to confirm the diagnosis. Comprehensive laboratory diagnostic procedures are designed to identify the causative virus or the viral component of the specific antibodies it induces. Laboratory costs for measuring antibody titres in serum are low compared with those for histopathology, virus isolation and molecular testing. However, estimates of antibody titres in individual serum samples are limited and sometimes very unreliable, thus, serum must be collected from several animals in the acute and convalescent phases to properly assess the association between seroconversion and disease, but the total cost of such diagnostic tests can be very high. The assessment of immunity during BHV-1 diagnosis is made by the indication of specific receptor molecules – immunoglobulins IgA, IgM and IgG (Immunoglobulin A, M, G), which are consistently synthesised in recurrent herpes virus, becoming crucial for protection against infection. In the presence of complement, antibodies neutralise the extracellular virus, but complement deficiency increases the susceptibility of the animal to infection. When the BHV-1 virus is not confirmed by antibodies, it can be an intracellular virus, in which case virus multiplication is inhibited by cellular factors such as T-lymphocytes, macrophages, and polymorphonuclear leukocytes. On the one hand, cellular immune factors cause lysis of infected cells, promoting the escape of intracellular virus and its subsequent neutralisation by antibodies, and on the other hand, cellular immune factors affect neighbouring normal cells, preventing them from becoming infected. Antibody development and the cellular immune response are the result of the interaction between the virus, the cells responsible for immunity, namely the different subpopulations, lymphocytes without marker T cells or B cells, monocyte-macrophages and granulocytes, and their products.

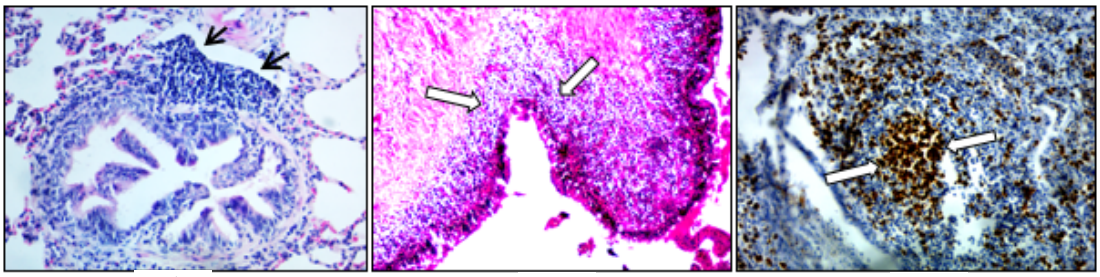
If the pathogen is identified in laboratory tests, the presence of histological tests for immunomorphological reactions provides confidence that the pathogen is indeed causing disease in the animal. Calves that presented clinical signs of infectious rhinotracheitis were tested with PCR tests for the BHV-1 virus. Tracheal histosections from a clinically healthy calf of 4 months of age are presented in Figure 1 (a). The control group represents histosections from healthy animals that were PCR-negative and had unchanged tracheal mucosa. The tracheal tissue of calves infected with IBR-1 at the age of 4 months is presented in Figure 1 (b). Changes in the tracheal mucosa and its lamina were identified; the glands were infiltrated with lymphocytes, plasmocytes, histiocytes and neutrophils. In histosections of trachea samples from IBR-1-infected calves aged 4 months, active mitosis of lymphoblasts, which were detected in the centre of the lymphoid tissue associated with the tracheal mucosa (Fig. 1 (c)), was observed when staining with the PAP method using the monoclonal antibody Anti-PCNA.



a) b) c)

Figure 1. *Tissue samples of the trachea of a four-month-old calf: a) Control group; b) In IBR. Haematoxylin-eosin staining; c) In IBR. PAP method, Anti-PCNA monoclonal antibody, Clone PC10. Microscope magnification* ×200
Source: *compiled by the authors*

Immunomorphological analyses of the bronchial system of clinically healthy animals and calves with IBR-1. Figure 2 (a) Histosection specimens from a clinically healthy calf aged 4 months present bronchial mucosa without any changes. The lymphoid tissue associated with the bronchial system is in a state of relative quiescence, as delineated by the arrows. Figure 2 (b) demonstrates hyperplasia of bronchus-associated lymphoid tissue, disintegration of bronchioles walls with their replacement by connective tissue, lung parenchyma along bronchiolar system infiltrated with plasmocytes, lymphocytes, macrophages and neutrophils. Figure 2 (c) using the PAP method and the monoclonal antibody Anti-PCNA, labelled histosection specimens of trachea from IBR-1 infected calves aged 4 months. Hyperplasia of broncho-associated lymphoid tissue and active proliferation of lymphoblasts were established, which is emphasised by white arrows.

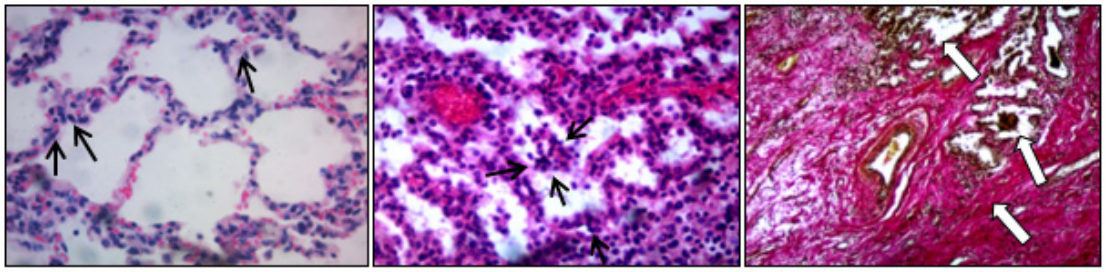


a) b) c)

Figure 2. *Tissue samples of the bronchial system of a four-month-old calf: a) Control group; b) In IBR. Haematoxylin-eosin staining; c) In IBR. PAP method. Anti-PCNA monoclonal antibody, Clone PC10. Microscope magnification* ×200

Source: *compiled by the authors*

Immunomorphological analysis of lung parenchyma from clinically healthy calves and IBR-1-infected calves is demonstrated in Figure 3. The control group, marked in Figure 3 (a), was characterised by free alveolar cavities with isolated macrophages, as indicated by the black arrows. In addition, macrophages and small lymphocytes were located in the walls of the alveoli. Figure 3 (b) presents lung tissue samples from IBR-1 infected calves at 4 months of age. Numerous cubic alveolocytes are identified and the lumen of the alveoli contains sloughed alveolocytes, macrophages and necrotic mass as indicated by the black arrows. Figure 3 (c), the Van Gieson method demonstrates fibrosis of lung parenchyma and disintegration of alveoli in IBR, which is marked by white arrows.

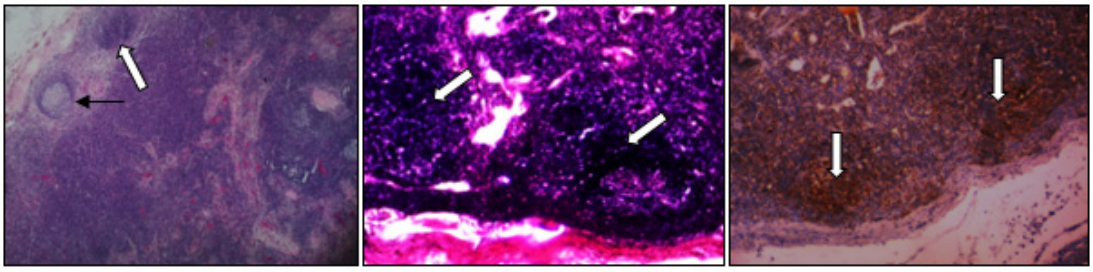


a) b) c)

Figure 3. *Tissue samples of lung alveoli of a four-month-old calf: a) Control group; b) In IBR. Haematoxylin-eosin staining; c) In IBR. Van Gieson's staining method. Microscope magnification* ×400

Source: *compiled by the authors*

Immunomorphological analysis of regional lymph nodes of lungs of clinically healthy calves and IBR-1 infection is presented in Figure 4. Figure 4 (a) in the control group calves lymph nodes demonstrate lymphoid follicles with light centres marked with black arrows and lymphoid follicles without light centres marked with white arrows. Figure 4 (b) in IBR demonstrates hyperplasia of the B-dependent zone of lymph nodes, where the number and size of lymph follicles with light centres are increased, and active mitosis of lymphoblasts in the light centre of lymph follicles is observed. In addition, hyperplasia of the T-dependent zone of lymph nodes is noted. In Figure 4 (c) using the PAP method with monoclonal antibody Anti-PCNA, active proliferation of lymphoblasts in the luminal centre of lymphoid follicles and hyperplasia of B-dependent zone of lymph nodes, which are indicated by white arrows, were identified in IBR.



a) b) c)

Figure 4. *Tissue samples of regional lymph nodes of lungs of a four-month-old calf: a) Control group; b) Serous purulent lymphadenitis in IBR. Haematoxylin-eosin staining; c) In IBR. PAP method. Anti-PCNA monoclonal antibody, Clone PC10. Microscope magnification* ×100

Source: *compiled by the authors*

Analysis of the obtained data in Figure 4 demonstrates that B- and T-dependent zones of regional lymph nodes are actively functioning, indicating the development of humoral and cellular immune response to IBR-1. Figure 5 presents an immunomorphological analysis of the spleen of clinically healthy animals and young cattle infected with IBR-1. Figure 5 (a) presents a red circle – T-dependent periarterial zone and a green circle – B-dependent zone of spleen white pulp in calves of the control group. Figure 5 (b) demonstrates hyperplasia of the white pulp of the spleen in IBR, where the T-dependent zone demonstrates clusters of lymphocytes around vessels, and the B-dependent zone has no distinct lymphoid follicles. In the red pulp, the presence of erythrocytes, lymphocytes, macrophages, plasma cells, neutrophils and blast cells can be seen. As noted in Figure 5 (c), IBR demonstrates active proliferation of lymphoblasts in the T-dependent zone, while in the B-dependent zone, there are only isolated lymphoid follicles with weak proliferation of lymphoblasts.

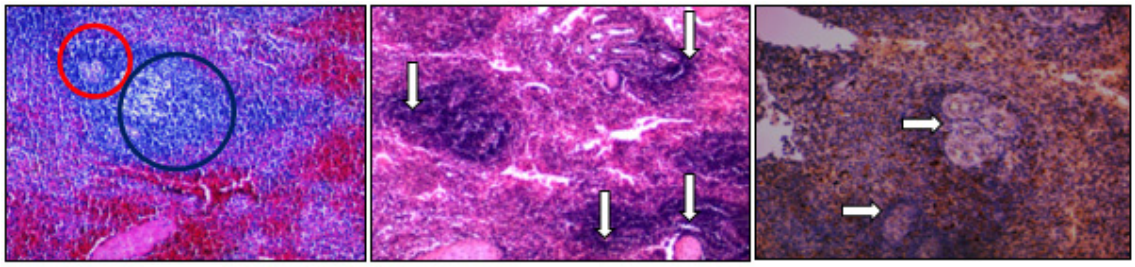


Figure 5. *Spleen tissue samples of a four-month-old calf: a) Control group. Red circle indicates T-dependent periarterial zone, blue circle B-dependent zone in the form of lymphoid follicles; b) In IBR. Haematoxylin-eosin staining; c) In IBR. PAP method. Anti-PCNA monoclonal antibody, Clone PC10. Microscope magnification* ×100

Source: *compiled by the authors*

The results of the spleen examination indicate that T-dependent sites are more active and are responsible for the development of the body's cellular immune response. It appeared that trachea-associated lymphoid tissue is closely related to the presence of herpesvirus BHV-1 pathogen. IBR-1 is morphologically manifested by hyperplasia of lymphoid tissue, an increase in the number of lymphocytes, plasma cells and immunoblasts in the centre of the lymphoid tissue, and its distribution over the entire area of contact with the mucous membrane, infiltration of the trachea and tracheal glands with lymphocytes, plasma cells and macrophages. In addition, the research confirmed that with the active participation of herpesvirus BHV-1, there is a change in broncho-associated lymphoid tissue, which is morphologically accompanied by its hyperplasia and infiltration of the bronchial system and alveolar walls with lymphocytes, plasma cells and macrophages. It was established that infection of four-month-old calves with IBR-1 virus leads to follicular hyperplasia of regional lymph nodes with subsequent atrophy as the disease progresses. Histopathologically, it is expressed by a decrease in the number of lymphoid follicles, and thinning of the paracortical zone, i.e. atrophy of B- and T-dependent zones of lymph nodes.

DISCUSSION

The various causes of respiratory diseases of cattle coincide in their clinical manifestation, but when making a definitive diagnosis, require mandatory pathological autopsy and pathohistological studies. The respiratory form of IBR-1 requires careful examination of the bronchi and bronchioles of the lungs, which are represented by inflammation of the mucous membrane of the upper respiratory tract, emphysema, frothy fluid in the bronchioles and bronchopneumonia. The results of this research corroborate the findings reported by D. Aniţă *et al.* (2010), where immune cells of the trachea, pulmonary-bronchial system, regional lymph nodes and white pulp of the spleen are directly involved in the pathogenesis of the respiratory form of IBR-1 in calves. The research established that infectious bovine rhinotracheitis is IBR-1, a febrile disease caused by a primary viral infection, which is usually accompanied by respiratory distress, tracheal vesiculation, tracheal mucosal lesions covered with exudate of mucus, pus and fibrin. Based on the experimental data of R. Mandelik *et al.* (2021), it was found that in IBR-1, extrudates are easily removed from the tracheal mucosa, exposing a smooth and intact membrane, whereas in bronchopneumonia, multifocal pale areas and mucosal necrosis are observed. Massive keratoconjunctivitis and sometimes encephalitis may occur in young animals. Some IBR-1 strains cause acute gastroenteritis, which is difficult to distinguish from dyspepsia and enterotoxemia.

The results of the histological analysis confirmed the data obtained at autopsy and demonstrated the presence of changes not detectable at macroscopic examination. Assessing immunomorphological reactions in the lungs of 4-month-old calves infected with IBR-1, it was noted that there were numerous cube-shaped alveolar cells near the alveolar wall, and in the lumen of the alveoli they were exfoliated; the presence of macrophages and necrotic masses on fibrotic parts of the

lung parenchyma was noticeable. In the pathological anatomical research of S. Comakli *et al.* (2019), lobular, serous and serous haemorrhagic pneumonia were observed in calves infected with the respiratory form of IBR-1. The lungs presented with white thick bronchial secretions and cavities of various sizes that were filled with white contents. In most cases, these changes were found in the cephalic and middle lobes of the lungs. In severe cases, pulmonary gangrene with putrefactive pleurisy, dilated haemorrhages and intra-alveolar oedema were observed. EFSA AHAW Panel *et al.* (2017b) indicated that in the respiratory form of IBR-1, necrosis, desquamation and atrophy of lymphoid tissue, hyperplasia of the T-dependent zone of the white pulp of the spleen was observed in the spleen of calves. Notably, these areas are more active and responsible for the development of the cellular immune response of the organism.

IBR-1 is initiated by multiple viruses and is, therefore, a multipathogenic respiratory disease of cattle that causes bacterial pneumonia; when infected sexually in adults, infectious pustular vulvovaginitis; and the keratoconjunctival form in calves. It is believed that IBR-1 is a disease in which the viral genome fuses with the genome of the host cell, causes immune dysfunction, and the organism is completely neutralised from viral infection, but the stress factor increases the incidence of the disease and on the background of reduces resistance. The results of these observations confirm the data of N. Beristain-Covarrubias *et al.* (2019), IBR-1 causes acute morbidity of about 75% and more than 50% mortality of cattle in farms due to secondary infections. The natural gateway for entry of BHV-1 is the mucosa of the upper respiratory tract. Inflammatory processes in infectious rhinotracheitis led to hemostasis disorders, changes in blood properties, increased platelet aggregation, and developing microvascular thrombosis in various organs and tissues, such processes were observed in the trachea and lungs.

At agricultural cattle breeding and rearing enterprises in Kyrgyzstan, live vaccines "TRIVAK", "BOVILIS" and "HYPRABOVIS-4" are used for the prevention of IBR-1 in cattle, but the possibility of residual vaccine viruses in immunised animals should be considered. According to A.E. Erdem and B. Sareyyüpoğlu (2022), adherence to a four-year vaccination schedule reduces the incidence of disease in the herd and minimises the number of virus carriers. Successful eradication of IBR-1 has been achieved in Denmark, Finland, Norway, Sweden, Austria, Switzerland and parts of Italy by adopting a strategy of separating infected animals and Differentiating Infected Vaccinated Animals (DIVA). Vaccines usually prevent the development of clinical signs and significantly reduce virus spread after infection, but do not completely prevent infection. L.F. Garcia *et al.* (2020) inform that in moderate epidemics of the BHV-1 virus, it is reasonable to use a labelled vaccine lacking specific glycoprotein gE (Glycoprotein E) antibodies to vaccinate up to 5% of positive animals in a herd, followed by culling. Parenteral administration of a mutant viral vaccine with deleted gE in BHV-1, used in combination with diagnostic testing and targeted culling according to a strategy of testing and slaughter of seropositive animals infected with field strains, has led to the eradication of the disease in some European countries.

Vaccination of cattle against BHV-1 herpesvirus is a priority in meat production in Kyrgyzstan. Most vaccines are administered intramuscularly or intranasally from 20 days of age, depending on the type of antigen, and the timing of vaccination is determined by the calendar of preventive measures on the farm. As the research of J. Baruch *et al.* (2019) demonstrates, the following rules must be observed to maximise vaccine efficacy: only vaccinate healthy animals; vaccinate before herd selection, considering that the immune response develops on day 14; plan revaccination of calves during the weaning period, as immunisation with colostrum affects the effectiveness of prophylaxis; heifer cows should be vaccinated 2-4 weeks before calving. As reported in research by B.W. Newcomer (2021), economic losses in infectious rhinotracheitis: under-fertilisation due to abortions and stillbirths is in the range of 5-30%; birth of non-viable calves about 10%; decrease in milk yield during the disease in the range of 50-60%; mortality of young animals from serous pneumonia is about 20%; under-receipt of live weight gain in young animals – 50-70%; increase in the number of cows with multiple unfertilised inseminations up to 30%; reduction of calf yield per 100 cows by 5-10%.

The study demonstrated that IBR-1 causes significant economic losses to livestock production and is associated with multi-organ infections leading to severe morbidity and mortality, therefore, it is important to find inexpensive and practical methods that allow selective detection of the BHV-1 antigen. In addition, it is advisable to establish an IBR-1-free breeding herd by gradually removing herpes-positive animals from regular breeding lots and replacing them with healthy calves. In farms in Kyrgyzstan that have experienced an outbreak of herpesvirus BHV-1, the purchase and sale of cattle, regrouping of animals, and export of forage, care items and milk products from sick animals without prior disinfection are prohibited. Sick animals shall be assigned to separate service personnel. Carcasses of slaughtered animals are sold without restrictions if there are no anatomical changes. It is forbidden to buy and sell livestock, rearrange livestock, move feed, care for sick animals and export dairy products on farms where herpesvirus BHV-1 has occurred without prior disinfection. Sick animals should be segregated in a separate attendant. Carcasses of slaughtered animals can be sold without restrictions if there are no anatomical changes. Milk from clinically sick IBR-1 cows is pasteurised at 70°C for 30 minutes, while milk from

clinically healthy animals is used without restrictions. Farm restrictions are lifted after the animals have recovered and veterinary and sanitary measures have been completed, but not earlier than 30 days after the last vaccination.

CONCLUSIONS

As a result of the conducted research, it was established that since IBR-1 is the most widespread viral disease of cattle, its pathomorphological signs need more detailed investigation. IBR-1 of cattle causes significant economic damage to production and it is necessary to make a timely diagnosis and conduct effective therapeutic and prophylactic measures. Clinical examination of calves identified typical signs of the respiratory form of infectious rhinotracheitis in cattle: increased body temperature by 1.5-2°C, hyperemic nasolabial triangle, serous conjunctivitis, serous catarrhal rhinitis, dry cough, eventually changing to wet cough, rapid breathing, predominantly abdominal type with rales. To qualitatively diagnose infectious rhinotracheitis in cattle, PCR assays for the presence of infectious disease in agricultural farms were analysed. Calves with clinical signs of infectious rhinotracheitis were tested by PCR tests for the BHV-1 virus, which was positive in 100% of cases.

Histological examination of the lungs in the majority of calves indicated serous-neutrophilic pneumonia with pyogenic bronchiolitis. The respiratory form of IBR-1 in calves included hyperplasia of lymphoid tissue in the bronchi of the trachea and lungs, hyperplasia of B- and T-linked areas of regional lymph nodes in the lungs and hyperplasia of T-linked areas of white pulp in the spleen. In addition, IBR-1 in calves demonstrates dense infiltration of lymphocytes, macrophages and plasma cells in the affected organs of the trachea and lungs. There is hyperplasia of lymphoid tissue in the trachea, bronchial system of the lungs, regional lymph nodes of the lungs and corresponding areas of the spleen. In some calves, the respiratory form of IBR-1 resulted in fibrosis of pulmonary foci, with complications in the form of serous pyogenic inflammation of the trachea and lungs. The data on histopathological changes in lymph nodes of the lungs and spleen of calves in the acute form of IBR-1 were clarified and supplemented.

The main means of controlling BHV-1 is routine vaccination, which prevents clinical manifestations of the disease in the vaccinated person, and protection of the foetus from infection and careful analysis of the epizootic situation in the farm. For qualitative diagnosis of infectious rhinotracheitis in cattle, it is necessary to comprehensively analyse the IBR-1 situation in farms, distinguish clinical signs of infectious diseases in animals, and conduct a thorough evaluation of the results of serological, pathological, and histological studies. From the standpoint of relevance and usefulness of the investigation described in this research, further investigation of IBR-1 herpesvirus and its new strains as frequently occurring diseases of cattle on modern farms seems promising.

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CONFLICT OF INTEREST

None.

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Анотація. Концентрація худоби на обмежених територіях, порушення режиму харчування, дисбаланс мікро- та макроелементів сприяють пригніченню природної резистентності організму, недостатньому набору живої маси тварини, що призводить до зростання інфекційних захворювань молодняка з високими показниками вимушеного забою та падежу худоби. Джерело збудника інфекції ринотрахеїту – герпевірус великої рогатої худоби *Bovine alphaherpesvirus 1* – перешкоджає розвитку тваринницької галузі, тому необхідно шукати можливі підходи щодо профілактики та контролю даної інфекції. Метою дослідження є визначення імуноморфологічних змін у лімфоїдній тканині трахеї та бронхіальної системи, у регіонарних лімфатичних вузлах легень і в селезінці

в телят, які природно хворі на інфекційний ринотрахеїт. В основу експериментальних досліджень покладено вивчення імуноморфологічних реакцій у лімфоїдній тканині під час інфікування молодняка великої рогатої худоби вірусом *Bovine alphaherpesvirus 1*, із застосуванням полімеразної ланцюгової реакції, гістологічних та імуногістохімічних методів. За результатами досліджень встановлено, що в трахеї спостерігалася гіперплазія трахеє-асоційованої лімфоїдної тканини, а в легенях – гіперплазія бронхіально-асоційованої лімфоїдної тканини, при цьому уражені ділянки трахеї та легень були інфільтровані лімфоцитами, макрофагами та плазматичними клітинами. В імуноморфологічних реакціях реґіонарних лімфатичних вузлів відзначають гіперплазію В- і Т-залежних зон, а в селезінці – гіперплазію Т-залежних зон білої пульпи. Таким чином, імунокомпетентні клітини лімфоїдної тканини, асоційовані з В- і Т-залежними ділянками трахеї, бронхіальної системи легень і реґіонарних лімфатичних вузлів легень, а також з Т-залежними ділянками селезінки, беруть безпосередню участь у патогенезі інфекційного ринотрахеїту телят респіраторного типу. Антибактеріальна терапія антибіотиками знищує патогенну та нормальну флору в кишечнику, але недостатньо ефективно діють на вірусну інфекцію, тому виробничі випробування ефективних засобів специфічної профілактики та вакцинації є першочерговим завданням ветеринарії

Ключові слова: велика рогата худоба; герпевірус; полімеразна ланцюгова реакція; патологія; імуноморфологія; асоціативні хвороби