Ukrainian Journal of Ecology

Ukrainian Journal of Ecology, 2019, 9(2), 217-226

ORIGINAL ARTICLE

UDC 619:612.017:619:615.37:636.92

Structural and functional features of the vermiform appendix at the tissue and cellular levels in rabbits after the introduction of immunobiological drugs

Ya.V. Kisera, Yu.G. Storchak, B.V. Gutyj, L.Ya. Bozhyk, N. Magrelo, Y. Sus, O. Dashkovskyy, V.I. Pryimych, U. Vus, L. Kit, R. Sachuk

Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv, Pekarska Str., 50, Lviv, 79010, Ukraine.

E-mail: juliettus1@gmail.com

Received: 22.05.2019. Accepted: 18.06.2019

Despite a widespread introduction of immunoprophylaxis, the national scientific literature doesn't frequently deal with the data containing a detailed description of the morphological state of the immune system's central and peripheral organs, as well as their immunomorphological rearrangement after the use of vaccines and the effects of immunostimulants. It is also worth noting that such organ of the peripheral immune system as a vermiform appendix was mainly ignored by the domestic scientists. We did not find a detailed description of the morphological changes of the rabbits' vermiform appendix that occur after the introduction of immunobiological drugs. We conducted the histological studies of the vermiform appendix of rabbits after performing an antigenic stress using the vaccine against streptococcal and staphylococcal infections of animals along with the preventive agent "Pneumo-Pro" separately and combined with Selefer, a selenium-containing immunostimulant. The structural changes in the lymphoid apparatus, as well as in the structural elements of the mucous membrane and submucosal basis were noticed after the use of immunobiological drugs. In particular, an expressed hyperplasia of lymphoid elements develops. The infiltration of plasma by submucosal cells was noted too. An increase in the number of exocrine cysts was also observed. The amount of mucus increases on the surface of the mucous membrane. Development of hyperemia and stasis was noted in blood vessels.

Keywords: Lymphoid nodes; crypts; lymphocytes; B-lymphoblasts; macrophages; epithelial cells; plasma and exocrine cells

Introduction

The vermiform appendix is a lymphoepithelial organ that performs a protective function and relates to the peripheral part of the immune system. The development, proliferation and differentiation of immunocompetent cells occurs inside this important formation, first and foremost, of B-cell subpopulations (Dasso et al., 2000; Gutyj et al., 2017; Khariv et al., 2018; Kysera et al., 2018). Vermiform appendix is sometimes called the tonsils of the abdominal cavity due to the high concentration of lymphoid cells in it. The mucous membrane, as well as the submucosa of the vermiform appendix, are infiltrated by lymphocytes, which form lymph nodes and interstitial clusters. The muscle membrane consists of the inner circular layer and the outer longitudinal one. The latter is a solid one. It is covered with a serous membrane outside that forms an own mesentery of the vermiform appendix.

The vermiform appendix is a part of the lymphoid formations that accompany the intestine and among mammals is considered to be the most likely analogue of the birds' bursal sac. The lymphoid tissue of the vermiform appendix usually occupies the tunicas/mucosa of the appendix's wall, but often extends to the entire tunicamucosa. The gentle stroma of the lymphoid tissue is formed by a mesenchial reticular tissue, however, intestinal epithelium is involved in the formation of stroma too (Bakhmet, 2008; Bibik and Berest, 2011).

A layer of nodulus lymphaticus and interfollicular lymphoid tissue are located in the loops of the gentle stroma. Each of the appendix's nodes is made up of three divisions: 1) the upper one, adjacent to the crypts; 2) the middle one; 3) the basal one, directed to the tunicamuscularis that sometimes penetrates the serous membrane of the appendix. A light reproduction center is located in the basal division. The middle division contains small lymphocytes which are located in a light center in the form of a hat. The upper division contains small lymphocytes that migrate to the epithelium of the crypts (Vorob'eva, 2017).

Since the vermiform appendix is considered analogous to the primary lymphoid organ for B-lymphocytes, then it has a feature that distinguishes it from the primary T-body, i.e., thymus. Antigens do not penetrate the thymus, while in the

appendix there is a massive portion of the microbial antigen that is absorbed by the lymphoid tissue macrophages, first interfollicular and after the intrafollicular ones. The similarity with thymus is either in the complete absence or in a very small number of plasma cells located in the appendix's lymphoid tissue (Kooij et al., 2016). A partuicularly large number of intrafollicular cells is found in lymphoid follicles of the rabbit's appendix. (Ljubovceva, 2009).

Approximately 30% of all immunocompetent intestinal cells is concentrated in the tunicamucosa of appendix. About 25% of tunicamucosa consists of immunologically active tissue. Lymphoid nodules of the appendix (noduli lymphoidei app) are located diffusely (in tunica mucosa, tunica s/mucosa) (Galeeva, 2012; Kostilenko and Grin', 2012).

Nodulus lymphaticus lymphocytes of the appendix are located under the mucosal layer interacting with the epithelial cells. These lymphoid clusters are called MALT – mucosa-associated lymphoid tissue.

Reproductive centers are located in the lymphoid nodules of the vermiform appendix. Here the reproduction of lymphocytes occurs, which are of great demand in the places of a constant antigenic penetration. Depending on the localization of the lymphoid tissue associated with the mucosal layer, a term GALT (gut-associated lymphoid tissue) is used, indicating the lymphoid formations of the mucous membranes associated with the intestine.

The clusters of lymphoid tissue associated with the mucosal layer are involved in specific immunity and participate in the activation of B-lymphocytes that differentiate into plasma cells. These plasma cells synthesize specific antibodies that belong to IgA, IgM and IgG. Mature plasma cells appear on the 15th day after birth and preserve throughout the whole life. Cells that secrete IgM are dominant and are placed mainly in the central divisions of the lymphoid nodules. There is a slightly smaller number of plasma cells that secrete IgA and IgG. They are located along the periphery of the lymphoid nodes, as well as between the crypts (Kuz'mina, 2014).

The composition of the lymphoid nodules of the vermiform appendix is represented by the cells of the lymphoid series of various maturity degree. The dome of the appendix nodules contains large, medium and small lymphocytes, as well as macrophages. Young and mature lymphocytes densely populate the crown of the lymphoid nodule.

Appendix's lymphoid nodes, along with the cells of the lymphoid series, contain a large number of macrophages with the particles of dead cells and bacteria inside. There are no mature plasma cells in the dome. Lymphoid nodules are covered with a specialized epithelium, capable of capturing an antigenic material. In the cell matrix there are structures resembling microtubules and microfibrils penetrating deep into the apical part of the cytoplasm. By their ultrastructural organization, these cells are similar to the so-called tufted cells found in the small intestine epithelium, as well as to the specialized M-cells of the epithelium of the lymphoid (Peyer) plaques that take part in the transport of antigen from the small intestine's lumen to the immunocompetent cells. B-lymphocytes in the dome are at different stages of maturity and differentiation (Murphy et al., 2011).

The peculiarities of functioning of the lymphoid tissue associated with the intestine are that intact lymphocytes penetrate into the circulatory system, then pass into the appendix, where the process of priming develops. This means that under the influence of a special cytokine environment B-lymphocytes differentiate into cells, intended for the synthesis of sIgA. Such lymphocytes penetrate the mesenteric lymph nodes through the afferent lymphatic ducts and reach the spleen through the blood current where the differentiation of B-lymphocytes is carried out. Then they penetrate the organs containing tunicamucosa, for example, in tunica mucosa intestinum tenue and crasum, where they multiply intensively. This process is known as homing (Gorfu et al., 2009).

Lymphoid tissue of the vermiform appendix is a kind of barrier zone during the penetration of foreign agents through tunicamucosa. A function of recognition is typical for the lymphoid clusters of the appendix, which manifests itself in the interaction of the antigens with the immune system cells and a subsequent transferring of information to the thymus and bone marrow.

Newly formed lymphocytes and antibodies are not only used in their place of birth, but are also spread through the vascular bed, reaching the chest duct, lymph nodes and spleen. T-lymphocytes located in the breeding center of nodules can be distinguished from B-lymphocytes, since the latter have several nucleoli. The ratio of T- and B-lymphocytes varies from 1:8 to 1:28. The majority of lymphocytes have immunoglobulins on their surface, indicating their belonging to the B-cells. There is about 70% of such lymphocytes in the lymphoid tissue of the rabbit's appendix. Up to 52% of lymphocytes are involved in a socket formation, being stimulated by the complement. Appendix is an important organ for the formation of B-zones of the immune system organs in ontogenesis and is involved in immune responses (Kooij et al., 2016; Gutyj et al., 2016; Khariv et al., 2016).

A proof of the existence of immune activity of the appendix's lymphoid tissue may be a fact that in response to the introduction of antigens into the rabbits' organ lumen or its wall, an increase in the socket-forming characteristics of the organ's lymphocytes is observed. The antigen introduced during the experiments collapsed in the reproduction centers and in the dome of the lymphoid nodes by the macrophages located there. At the same time, immunization of rabbits leads to the growth of young and differentiated B-lymphocytes in the appendix's lymphoid tissue. In terms of microbial stimulation, the lymphoid nodes of the appendix are acting as peripheral organs of the immune system (Junqueira and Carneiro, 2005).

Since T- and B-lymphocytes, lysozyme and some other substances are located in the appendix, a protective function is carried out. (Velazquez et al., 2005). Entering the appendix, T- and B-lymphocytes differentiate into their subpopulations and having accumulated, form lymphoid follicles (Dasso et al., 2000; Hanson and Lanning, 2008).

The participation of the appendix in the immune system is also proved by the following fact. The positive reaction of the appendix's lymphocytes to the alkaline phosphatase and the negative reaction to the acid phosphatase allowed to make a conclusion on their predominant belonging to the B-dependent part of the immune system. (Smirnova et al., 2009; Petrenko, 2013).

The vermiform appendix is a densely innervated immunocompetent organ and has multifunctional properties like antigen-

independent differentiation of lymphocytes, which provides a natural resistance of an organism, immunity, immunological memory, immunological tolerance and reaction to specific pathological processes, as well as organism's secretory and hormonal functions. The appendix is involved in ripening of B-lymphocytes (Bahmet, 2008; Bibik and Berest, 2011). Also, the vermiform appendix is responsible for the endocrine function, since it synthesizes a number of enzymes that affect the digestive processes, as well as the activity of other organs of the abdominal cavity, synthesizing certain hormones (Gusejnov and Gusejnova, 2012).

It should be emphasized that the vermiform appendix hasn't enjoyed much attention of domestic scientists over the last years. Therefore, we set the goal to determine the structural and functional features of the vermiform appendix at the tissue and cellular levels in rabbits after the introduction of immunobiological drugs.

Materials and methods

The research was conducted at the Department of Normal and Pathological Morphology and Forensic Veterinary Medicine of the Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologies Lviv. 16 rabbits of two months of age were selected for the experiment according to the principle of analogues. 4 groups were formed (1 control and 3 experimental). Pnevmo-Pro, a prophylactic drug, was introduced to the animals of the first experimental group (Storchak and Kisera, 2015). Animals of the second experimental group were introduced a prophylactic drug "Pneumo-Pro" with the addition of an immunostimulator Selefer (Storchak and Kisera, 2015). Animals of the third experimental group were given an inactivated vaccine against streptococcal and staphylococcal infections (Ushkalov and Golovko, 2004). A physiological solution was injected to the control group of animals. Immunobiological preparations were introduced intramuscularly, twice at the intervals of 14 days at a dose of 0.5 ml for the first introduction and 1 ml for the second one. The animals were slaughtered on the 45th day.

The cutdown was performed using the Shor method (Goralskyi, 2005). For histological studies, pieces of the appendix were taken immediately after the animals' slaughter and fixed in a 10-12% cooling solution of neutral formalin followed by paraffin embedding according to the scheme offered by J. Kumar and L. Rudbeck (Kumar and Rudbeck, 2011). In order to detect the morphology of cells and tissues, Karachi hematoxylin and eosin staining, as well as methyl green and pyronin G staining by Brachet was used (Merkulov, 1996).

Results and discussion

According to the results of histological studies, it was found that the mucous membrane of the vermiform appendix of the control group of animals is covered by the well-noticeable shallow crypts, which extend in the direction of the submucosal basis. Lumen of some crypts is moderately wide, and narrowed in the others. Crypts do not contain foreign contents, are lined with a single-layer prismatic epithelium, which consists of columnar epithelium cells. Exocrinocytes, M-cells and enteroendocrinocytes are also available. Paneth cells, which contain acidophilic granules in the cytoplasm, are quite common at the bottom of the intestinal crypts. Undifferentiated (cambial) epithelial cells and endocrine cells are also located in this area (Figure 1).

Figure 1. Mucous membrane (1) and submucosal basis (2) of the vermiform appendix. Lymphoid nodules (3) are densely filled with cellular elements. *Hematoxylin-eosin × 100.*

The own plate of the mucous membrane passes into the submucosal basis without a sharp boundary. Numerous volumetric clusters of lymphoid tissue in the form of secondary lymphoid nodes are located in the plate and in the submucosal basis. They have large light reactive centers formed by proliferating lymphoblasts. Lymphoid follicles almost completely fill the intervals between the crypts and occupy a significant amount of the submucosal basis (Figure 2).

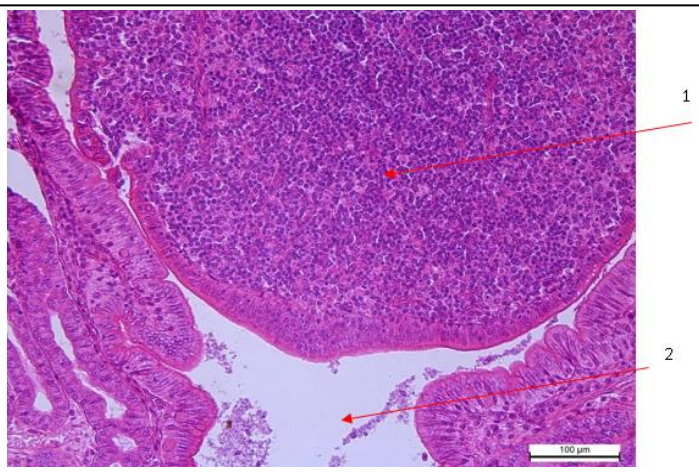

Figure 2. Lymphoid knot (1) of the vermiform appendix, which is in contact with the lumen of the intestine (2). A significant number of cellular elements in the lymphoid nodule is observed. *Hematoxylin-eosin × 200.*

An overwhelming majority of the secondary lymphoid follicles is cone-shaped. Crypts are located above the top of many follicles. Some secondary lymphoid nodes with a dome-shaped top touch the appendix's lumen. In the section indicated below, the lymphoid follicles are mainly covered with M-cells (Figure 3).

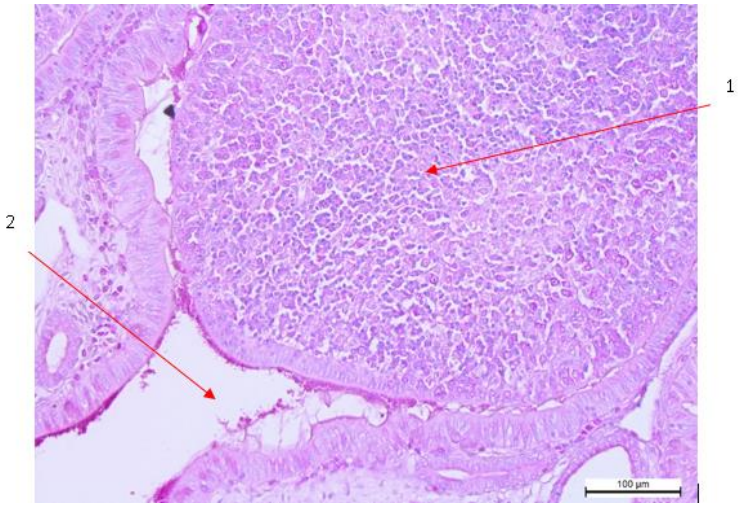

Figure 3. Lymphoid node (1) of the vermiform appendix that is in contact with the lumen of the intestine (2). A significant number of cellular elements in the lymphoid nodule is observed**.** *Methyl green and pyronin G by Brachet × 200.*

Cellular composition of the accumulated submucosal lymphoid nodules is heterogeneous. Proliferating B-lymphoblasts that form the reactive center are located in a very middle. There is a moderate amount of B-lymphocytes around the periphery. Interfollicular zones are predominantly filled with T-lymphocytes. Also, macrophages are available in the parenchyma of the accumulated submucosal lymphoid nodes. Interdigitating cells are sometimes observed. The vessels of the mucous membrane and submucosal basis are moderately expanded. The loose connective tissue contains fibroblasts, collagen, elastic and reticular fibers, as well as single lymphocytes and plasma cells. The number of lymphoid cells is slightly higher in the stroma, especially near the lymphatic follicles. The muscular membrane of the vermiform appendix includes two layers: the inner one is circular and the outer one is longitudinal. Appendix is covered with a serous membrane outside, formed by the loose connective tissue with a mesothelium, a single-layered flat epithelium, located above it.

Histological study of the vermiform appendix of the rabbits from the 1st experimental group (conducted on the 45th day after the introduction of the prophylactic drug "Pneumo-Pro") revealed that the mucous membrane is covered by the well-marked shallow crypts that extend in the direction of the submucosal basis. Lumens of some crypts are moderately wide, while the others are narrowed. The majority of crypts does not contain extraneous content, but few of them are filled with excessive amounts of mucus and desquamated cells (mainly enterocytes and exocrinocytes).

Both the own plate and submucosal basis contain numerous volumetric clusters of lymphoid tissue, which create accumulated submucosal lymphoid nodules, whose center is formed by the proliferating lymphoblasts (Figure 4). B-lymphocytes, macrophages and interdigitating cells are located on the lymphoblasts' periphery. Quite often, mitoses of lymphoid elements are visualized. Occasionally, lymphocytes undergo necrotic changes resulting in small gaps between the lymphoid cells (Figure 5).

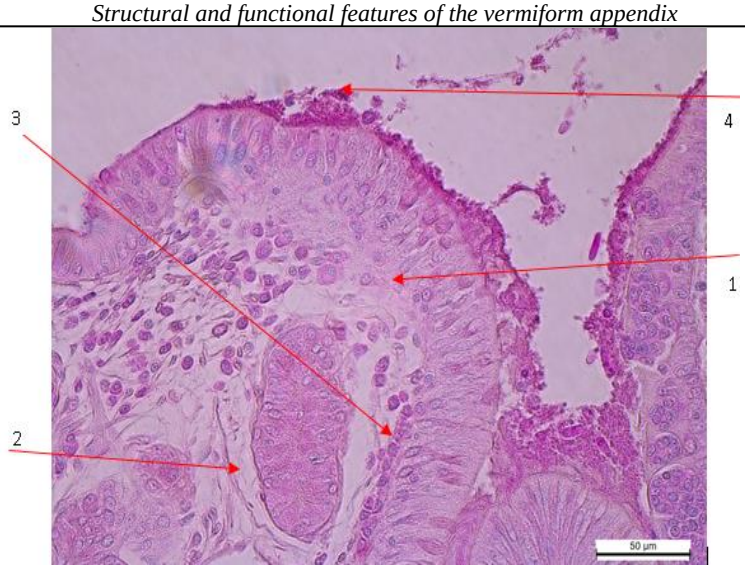

Figure 4. Infiltration of loose connective tissue of the mucous membrane (1) and submucosal basis (2) of the appendix by plasma cells (3). Increase in the amount of mucus (4) on the surface of the mucous membrane. *Methyl green and pyronin G by Brachet × 400.*

The peripheral part of the lymphoid nodules and the interfollicular zone contain a significant quantity of T-lymphocytes. An overwhelming majority of the secondary lymphoid follicles is cone-shaped. Crypts are located above the top part of many follicles. Some secondary lymphoid nodes with a dome-shaped top come in contact with the appendix's lumen.

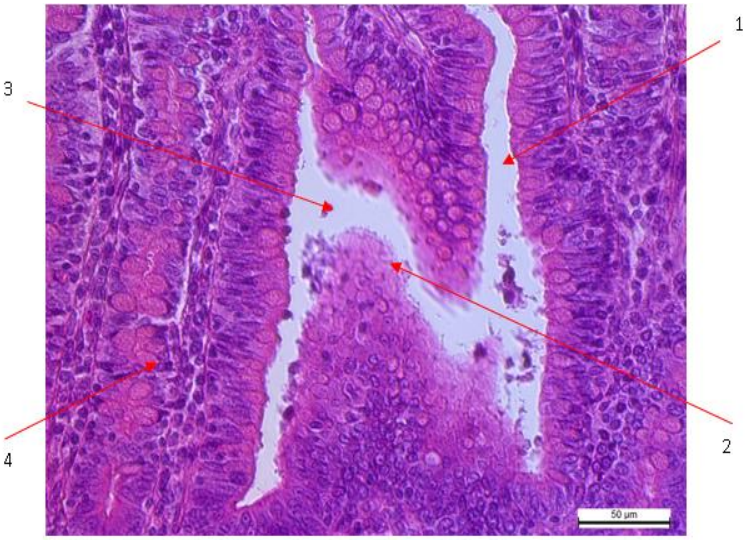

Figure 5. Increase in the number of exocrine cells in crypts (1) of the vermiform appendix. Desquamation of epithelial cells (2) into the crypts' lumen (3).Infiltration of the plate of the mucous membrane by lymphocytes (4). *Hematoxylin-eosin × 200.*

The vessels of the mucous membrane and submucosal basis are enlarged, filled with red blood cells and sometimes contain lymphocytes. Occasionally, gluing of red blood cells is recorded (Figure 6). Moderate perivascular edema is also observed. Individual vessels are full of lymphocytes. There are single lymphocytes, neutrophilic granulocytes and macrophages in the stroma, especially near the lymphatic follicles (Figure 7).

Figure 6. Expansion of the vessels (1) of the vermiform appendix's mucous membrane. Lymphocytes (2) and hemolysed erythrocytes are in the vascular lumen. *Hematoxylin-eosin × 400.*

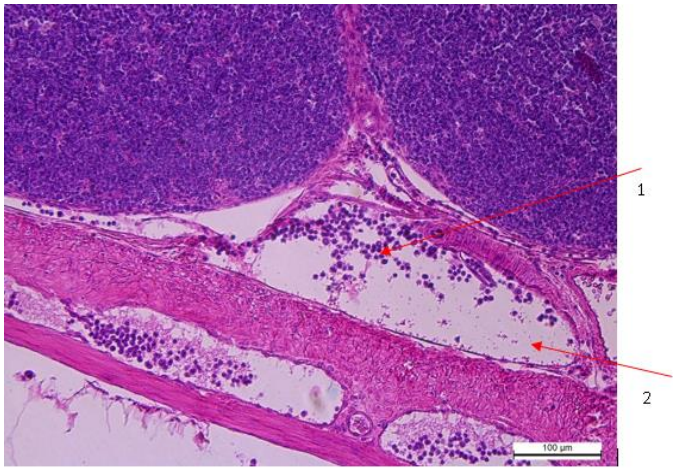

Figure 7. Expansion and overflow of appendix's wall vessels (2) by lymphocytes (1) *Hematoxylin-eosin × 200.*

The muscular membrane of the vermiform appendix includes two layers: the inner one is circular and the outer one is longitudinal one. The vessels of the intermuscular connective tissue are slightly enlarged, filled with erythrocytes and contain lymphocytes. The vermiform appendix is covered with a serous membrane outside, formed by the loose connective tissue with a mesothelium, a single-layered flat epithelium, located above it.

Histological study of the vermiform appendix of the rabbits from the 2nd experimental group (after the introduction of the prophylactic drug "Pneumo-Pro" with the immunomodulator Selefer) revealed a moderate expansion of individual crypts and an increase in the number of exocrine cells and mucus inside them. Most crypts are shallow, extending toward the submucosal basis (Figure 8). The lumen of some crypts is somewhat narrowed, th crypts do not contain extraneous content.

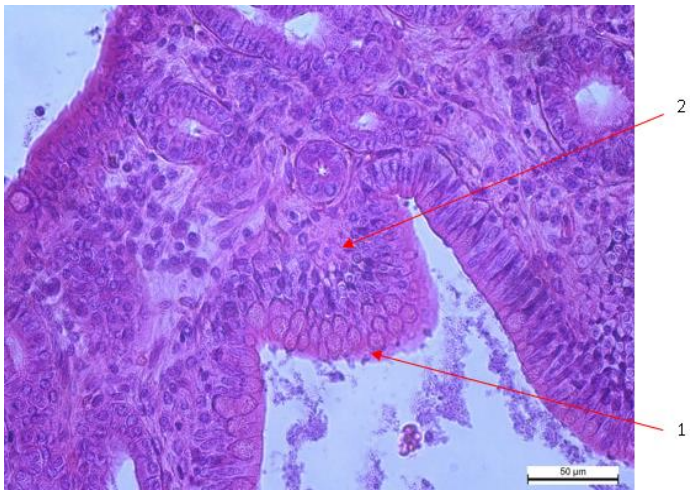

Figure 8. Moderate increase in the number of exocrinocytes (1) on the surface of the mucous membrane of the vermiform appendix. Polymorphic cell infiltration (2) of the plate of mucous membrane and submucosal basis is observed. *Hematoxylin-eosin × 400*.

Except of a single-layer columnar epithelium, the epithelial layer is saturated by exocrinocytes, M-cells and

enteroendocrinocytes. Paneth cells, which contain acidophilic granules in the cytoplasm, are sometimes observed at the bottom of the intestinal crypts. The undifferentiated (cambial) epithelial cells and endocrine cells are also located in this area. The vessels of the mucous membrane plate and submucosal basis are enlarged, overfilled with red blood cells and contain single lymphocytes. Loose connective tissue in the indicated area is moderately infiltrated by plasma cells, single lymphocytes and neutrophilic granulocytes (Figures 9 and 10).

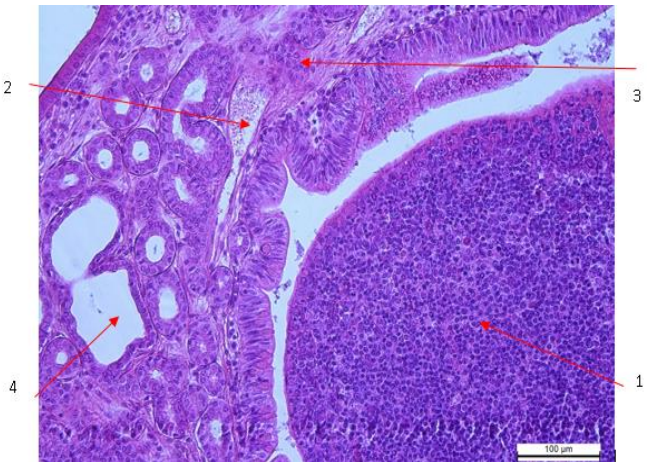

Figure 9. The lymphoid node (1) of the vermiform appendix densely filled with cellular elements. Moderately dilated vessels (2) of the mucous membrane. Insignificant polymorphic cell infiltration (3) of the mucous membrane plate and submucosal basis. Crypts with wide lumen (4). *Hematoxylin-eosin × 200.*

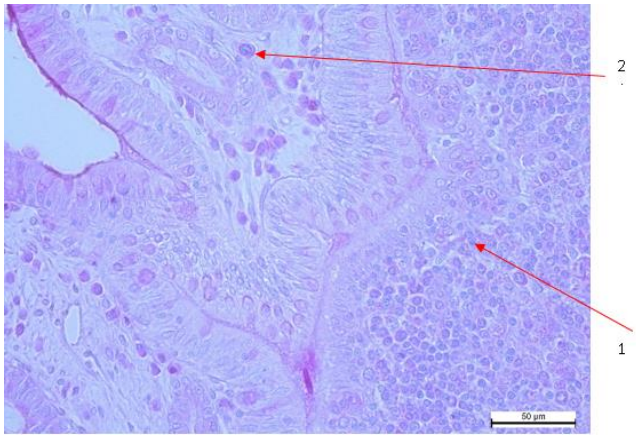

Figure 10. The lymphoid node (1) of the vermiform appendix densely filled with cellular elements. Moderate infiltration of the loose connective tissue of the mucous membrane and submucosal basis by plasma cells (2). *Methyl green and pyronin G by Brachet × 400.*

There are numerous volumetric clusters of lymphoid tissue both in the plate and submucosal basis in the form of submucosal lymphoid nodes, whose center is formed by proliferating lymphoblasts that create reactive centers. Interdigitating cells and macrophages are also visualized, some of which destroy necrotized lymphocytes. The quantity of T-lymphocytes increases in the peripheral and interfollicular zones. Some secondary lymphoid nodes with a dome-shaped top come in contact with the lumen of the vermiform appendix. The dome of such areas is covered mostly by M-cells (Figure 11).

The vessels of the mucous membrane of the submucosal basis are moderately dilated and somewhat filled with erythrocytes. Stroma is infiltrated by lymphocytes and neutrophilic granulocytes, especially near lymphatic follicles. The number of macrophages is somewhat increased.

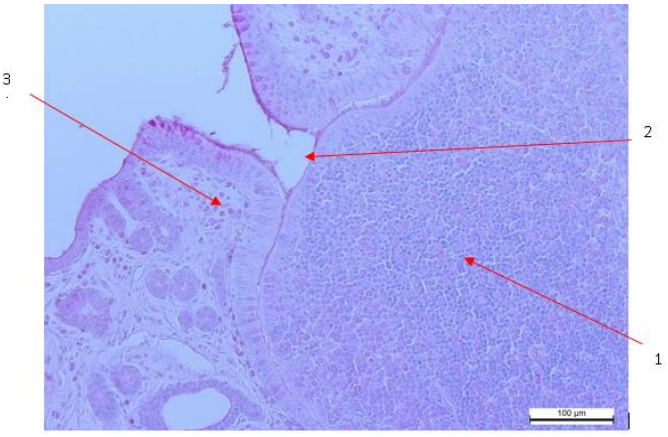

Figure 11. The lymphoid knot (1) densely filled with cellular elements, which is in contact with the lumen (2) of the vermiform appendix. Moderate infiltration of the loose connective tissue of the mucous membrane and submucosal basis by plasma cells (3). *Methyl green and pyronin G by Brachet × 200.*

The muscular membrane of the vermiform appendix comprises two layers: the inner one is circular and the outer one is longitudinal. The vessels of the intermuscular connective tissue are enlarged, overflowed with red blood cells. Perivascular edema also occurs. The vermiform appendix is covered with a serous membrane outside, formed by the loose connective tissue with a mesothelium, a single-layered flat epithelium, located above it.

Histological study of the vermiform appendix of the rabbits from the 3rd experimental group (conducted on the 45th day after the introduction of the inactivated vaccine against streptococcal and staphylococcal infections) revealed that its mucous membrane is covered with well-marked, shallow crypts extending in the direction of the submucosal basis. Lumen of some crypts is moderately wide and narrowed in the others. The increase in the number of exocrine and mucus is also observed (Figure 12). Some crypts also contain necrotized enterocytes and exocrinocytes.

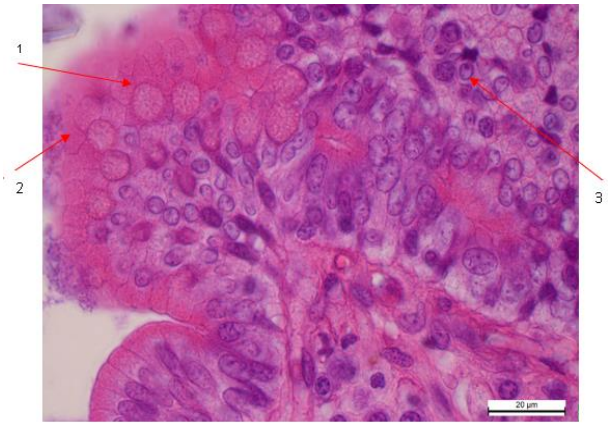

Figure 12. Increase in the number of exocrinocytes (1) on the surface of the vermiform appendix's mucous membrane (2). Infiltration of the mucous membrane plate by lymphocytes (3). *Hematoxylin-eosin × 1000.*

Congested submucosal lymphoid nodules of conical shape and loosely located lymphoid elements are situated both in the plate and submucosal basis. The number of lymphoblasts in the center of the congested lymphoid nodes is not substantial. Necrotic lymphocytes occur quite often. As a result, depletion of the lymphoid nodule cellular elements of the vermiform appendix is observed. Macrophages are visualized around necrotic lymphocytes (Figure 13). Also, the number of T-lymphocytes decreases in the interfollicular areas.

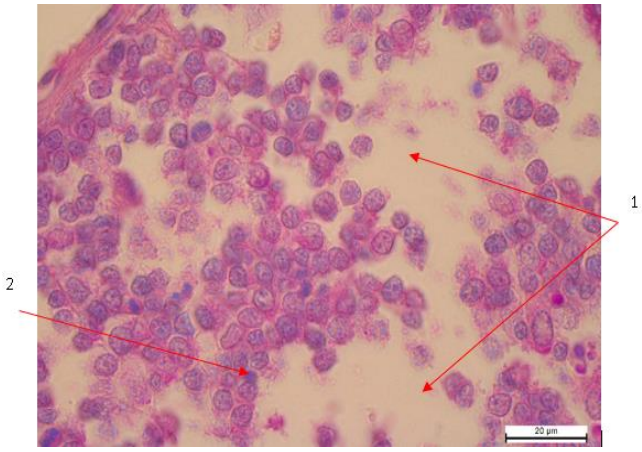

Figure 13. Decreased quantity of cellular elements (1) in the appendix lymphoid knot. Lymphocytes undergoing necrotic changes (2). *Methyl green and pyronin G by Brachet × 1000.*

The vessels of the mucous membrane and submucosal basis are expanded and filled with erythrocytes and lymphocytes. The quantity of lymphocytes increases dramatically in the stroma, especially near the lymphatic follicles. Infiltration by neutrophilic granulocytes is also observed (Figure 14).

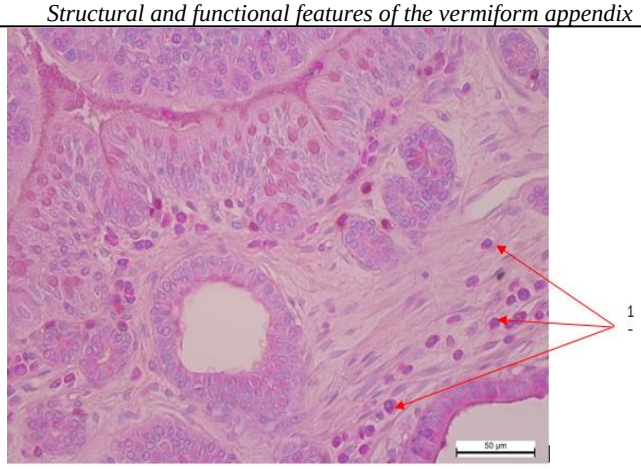

Figure 14. Infiltration of the vermiform appendix's mucous membrane plate by plasma cells (1). *Methyl green and pyronin G by Brachet × 1000.*

The muscular membrane of the vermiform appendix includes two layers: the inner one is circular and the outer one is longitudinal. Vessels of intermuscular connective tissue are enlarged, sometimes perivascular edema develops. The vermiform appendix is covered with a serous membrane outside, formed by the loose connective tissue with a mesothelium, a single-layered flat epithelium, located above it.

Conclusions

Histological studies of the rabbits' vermiform appendix performed after the parenteral introduction of immunoprophylactic drugs revealed significant structural changes in the lymphoid apparatus:

1) there is a significant amount of lymphoblasts in the center of submucosal lymphoid nodes; mitosis of lymphocytes is often visualized;

2) large, medium and small lymphocytes as well as macrophages locate in the dome of submucosal lymphoid nodes;

3) there are numerous volumetric clusters of lymphoid tissue that form submucosal clusters of lymphoid nodes in the plate and submucosal basis of the appendix;

4) the peripheral part of the lymphoid nodes and the interfollicular area contain a significant number of T-lymphocytes; the vast majority of secondary lymphoid follicles are cone-shaped;

5) appendix crypts contain a large number of exocrinocysts.

References

Bahmet, A. A. (2008). The effect of some immunopeptides on the immune structures of small intestinal lymphoid plaques. Rossijskij Zhurnal Gastrojenterologii, Gepatologii, Koloproktologii, 18(5), 38-44.

Bibik, E. Y., & Berest, A. Y. (2011). Sovremennye predstavleniya o morfogeneze pervichnogo limfoidnogo organa. Ukrainskiy morfologicheskiy almanakh, 9(3), 43-46.

Dasso, J. F., Obiakor, H., Bach, H., Anderson, A. O., & Mage, R. G. (2000). A morphological and immunohistological study of the human and rabbit appendix for comparison with the avian bursa. Developmental & Comparative Immunology, 24(8), 797-814. doi: 10.1016/S0145-305X(00)00033-1.

Galeeva, J. N. (2012). Sovremennye predstavlenija o plodnoj anatomii organov limfoidnoj sistemy cheloveka (obzor literatury)[Modern ideas about the fetal anatomy of the organs of the human lymphoid system. Vestnik novyh medicinskih tehnologij, 19(2), 384-400.

Goral's'kyi, L. P. (2005). Osnovy gistologichnoi tehniky i morfofunkcional'ni metody doslidzhennja u normi ta pry patologii. State Agroecological University. Zhitomir: Polissja (in Ukrainian).

Gorfu, G., Rivera-Nieves, J., & Ley, K. (2009). Role of β7 integrins in intestinal lymphocyte homing and retention. Current molecular medicine, 9(7), 836-850.

Gusejnov, T. S., & Gusejnova, S. T. (2012). Discussion of the anatomy of Peyer's small intestine plaques. Saratovskij nauchno-medicinskij zhurnal, 8(3), 687-691.

Gutyj, B., Grymak, Y., Drach, M., Bilyk, O., Matsjuk, O., Magrelo, N., Zmiya, M., & Katsaraba, O. (2017). The impact of endogenous intoxication on biochemical indicators of blood of pregnant cows. Regulatory Mechanisms in Biosystems, 8(3), 438-443. doi: 10.15421/021768.

Gutyj, B., Martyshchuk, T., Bushueva, I., Semeniv, B., Parchenko, V., Kaplaushenko, A., Magrelo, N., Hirkovyy, A., Musiy, L., & Murska, S. (2017). Morphological and biochemical indicators of blood of rats poisoned by carbon tetrachloride and subject to action of liposomal preparation. Regulatory Mechanisms in Biosystems, 8(2), 304-309. doi:10.15421/021748.

Gutyj, B., Paska, M., Levkivska, N., Pelenyo, R., Nazaruk, N., & Guta, Z. (2016). Study of acute and chronic toxicity of 'Injectable Mevesel' investigational drug. Biological Bulletin of Bogdan Chmelnitskiy Melitopol State Pedagogical University, 6(2), 174–180. doi: 10.15421/201649.

Hanson, N. B., & Lanning, D. K. (2008). Microbial induction of B and T cell areas in rabbit appendix. Developmental and

Comparative Immunology, 32(8), 980-991. doi: 10.1016/j.dci.2008.01.013.
Junqueira, L., & Carneiro, J. (2005). Basic histology: text and atlas. McGraw-Hill Medical, New York, USA.
Kamishnij, O. M. (2000). Osoblivosti morfogenezu brizhovyh limfatichnyh vuzliv bilyh shhuriv pislja antenatal'noji antygennoi stymuljacii. Ukrains'kyi medychnyi al'manah, 5, 83-85 (in Ukrainian).
Khariv, M., Gutyj, B., Butsyak, V., & Khariv, I. (2016). Hematological indices of rat organisms under conditions of oxidative stress and liposomal preparation action. Biological Bulletin of Bogdan Chmelnitskiy Melitopol State Pedagogical University, 6 (1), 276-289. doi: 10.15421/201615
Khariv, M., Gutyj, B., Ohorodnyk, N., Vishchur, O., Khariv, I., Solovodzinska, I., Mudrak, D., Grymak, C., Bodnar, P. (2017). Activity of the T- and B-system of the cell immunity of animals under conditions of oxidation stress and effects of the liposomal drug. Ukrainian Journal of Ecology, 7(4), 536-541. doi: 10.15421/2017_157.
Kooij, A., Sahami, S., Meijer, S. L., Buskens, C. J., & te Velde A. A. (2016). The immunology of the vermiform appendix: a review of the literature. Clin Exp Immunol, 186(1), 1-9. doi: 10.1111/cei.12821.
Kostilenko, Ju. P., & Grin', V. G. (2012). Strukturno-funkcional'naja harakteristika cherveobraznogo otrostka ljudej v vozrastnom aspekte. Mir mediciny i biologii, 8(2), 103-106 (in Russian).
Kumar, G. L., & Rudbeck, L. (2011). Immunogistohimicheskie metody: Rukovodstvo. Moscow (in Russian).
Kuz'mina, L. A., Parovichnikova, E. N., Mendeleeva, L. P., & Pokrovskaja, O. S. (2014). Transplantacija allogennogo kostnogo mozga pri hronicheskom mielolejkoze. Gematologija i transfuziologija, 59, 49 (in Russian).
Kysera, Ya. V., Storchak, Yu. G., & Gutyj, B. V. (2018). Experimental study of immunoprophylactic anti-pneumococcal medicine and its immunogenic properties. Ukrainian Journal of Ecology, 8(1), 307-316. doi: 10.15421/2018_216.
Ljubovceva, L. A., Efremova, O. A., Golubcova, N. N., & Russov, A. V. (2009). Svojstva granuljarnyh ljuminescirujushhih kletok. International Journal on Immunorehabilitation, 11(1), 25-26 (in Russian).
Merkulov, G. A. (1996). Kurs patologoanatomicheskoj tehniki. Izdatelstvo “Medicina”. Leningradskoe otdelenie (in Russian).
Murphy, K., Travers, P., Janeway, C., & Walport, M. (2011). Janeway's immunobiology, 7th edn. New York: Garland Science.
Petrenko, V. M. (2013). Funkcional'naja anatomija limfaticheskoj sistemy: sovremennye predstavlenija i napravlenija issledovanij. Mezhdunarodnyj zhurnal prikladnyh i fundamental'nyh issledovanij, 12, 94-97 (in Russian).
Smirnova, T. L., Sapozhnikov, S. P., Sergeeva, V. E., & D'jachkova, I. M. (2009). Nejromediatornoe obespechenie limfoidnyh i nelimfoidnyh organov v uslovijah jeksperimental'noj nejromoduljacii. Allergologija i immunologija. 10(1), 32-33 (in Russian).
Storchak, Ju. G., & Kisera, Ja. V. (2015). Patent Ukrainy na korisnu model' № 99020 Sposib vigotovlennja vakcyny dlja profilaktyky pnevmokokovoi infekcii teljat. № u 201413771; Bjul. № 9 (in Ukrainian).
Storchak, Ju. G., & Kisera, Ja. V. (2015). Patent Ukrainy na korysnu model' № 99019 Profilaktichnyi zasib dlja borot'by iz pnevmokokovoju infekcijeju teljat. № u201413768; Bjul. № 9 (in Ukrainian).
Ushkalov, V. O., & Golovko, A. M. (2004). Patent na korysnu model' № 41546 Ukraina. Sposib vygotovlennja vakcyny proty streptokokovyh ta/abo stafilokokovyh infekcij u tvaryn. Bjul. № 6 (in Ukrainian).
Velazquez, P., Wei, B., & Braun, J. (2005). Surveillance V lymphocytes and mucosal immunoregulation. Immunopathol. 26(4), 453-462.
Vorob'eva, N. F. (2017). Patomorfologicheskoe i immunogistohimicheskoe issledovanie struktur appendiksa posle allogennoj peresadki kostnogo mozga. Voronezh. Izdatel'sko-poligraficheskij centr “Nauchnaja kniga»” (in Russian).

Citation: Kisera Ya.V., Storchak Yu.G., Gutyj B.V., Bozhyk L.Ya., Magrelo N., Sus Y., Dashkovskyy O., Pryimych V.I., Vus U., Kit L., Sachuk R. (2019). Structural and functional features of the vermiform appendix at the tissue and cellular levels in rabbits after the introduction of immunobiological drugs. Ukrainian Journal of Ecology, 9(2), 217-226.
This work is licensed under a Creative Commons Attribution 4.0. License