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Morphological Characteristics of the Results of Experimental Modeling of Septic Peritonitis

Características Morfológicas de los Resultados del Modelado Experimental de Peritonitis Séptica

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SUMMARY: Experimental studies devoted to the study of the mechanisms of the pathogenesis of acute peritonitis and the development of new methods of medical and surgical treatment are becoming increasingly relevant. Today, experimental medicine knows many different ways to modeling septic peritonitis and eliminate it, but the role of the local immune system is underestimated, whereas it takes a direct part in inflammation. The objective of our work to study morphological features of results of experimental modeling of septic peritonitis in white rats. The study included 15 sexually mature white male rats weighing 276.75±6.56 grams. A simulation of septic peritonitis was performed by perforating the upper part of the cecum with four punctures with a G16 injection needle. As a result of the experiment, after examination of the peritoneal cavity, all 15 animals were diagnosed with omentum tamponade of perforated damage to the caecum. In 11 cases, the perforated wall of the caecum was covered by the greater omentum (73.34 %), and in the other 4 animals, tamponade was performed by one of the epididymal omentum (26.66 %). The initial stage of tamponade with the greater or epididymal omentums of a perforated caecum begins on the first day of the experiment and consists of tight interstitial consolidation between them, as well as in the invasion of blood vessels from the omentum side to the focus of infection, which ensure the delivery of the appropriate immunocompetent cells. As a result of this process, intensive lymphoid infiltrates are formed in this area, as well as the growth of adipose tissue, which isolates the inflammatory focus from the peritoneal cavity with a thick layer.

KEY WORDS: Peritonitis; Greater omentum; Duodenum; Stomach; Caecum; Testis; Lymph node; Lymphoid nodule; Lymphocytes; Adipocytes; Immunocompetent cells.

INTRODUCTION

Experimental studies on the mechanisms of the pathogenesis of acute peritonitis, the development and testing of the novel methods of medicamentous and surgical treatment of this pathology are becoming more and more relevant (Kebkalo *et al*., 2019; Liu *et al*., 2021). Experimental models of the peritonitis are crucial to obtain the reliable results. Currently, in experimental medicine, many different methods of modeling septic peritonitis are known (Sydorchuk, 2015; Vintrych *et al*., 2022; Brown *et al*., 2023). At the same time, in each case, the experiment should consider the optimal assessment of known etiological factors in its pathogenesis, among which the most common cases are ulcerative perforation of the stomach or duodenum, as well as perforation of the cecal appendage in its gangrenous inflammation (Hryn *et al*., 2022).

However, the role of the immune system has been underestimated, though it is directly involved into inflammation (Davis *et al*., 2017; Savchenko *et al*., 2018; Català *et al*., 2022; Kostylenko *et al*., 2022). The relevance of our study can be explained by the fact that in the scientific literature few publications on the clarification of morphological aspects of the reaction of local immunity in response to infection of the peritoneal cavity of experimental animals have been found. Therefore, the purpose of our work is to study the morphological features of the results of experimental modeling of septic peritonitis in albino rats.

MATERIAL AND METHOD

In this study 15 mature albino male rats, weighing 276,75±6,56 g, were involved into the experiment. All animals were kept in the standard conditions of the experimental biological clinic (vivarium) of Poltava State Medical University, in compliance with the regulations for keeping experimental animals adopted by the Directive of

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the European Parliament and Council (Directive 2010/63/ EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes, 2010), the Order of the Ministry of Education and Science, Youth and Sports of Ukraine as of 01.03.2012 No. 249 "On Approval of the Procedure for Conducting Experiments on Animals by Scientific Institutions" and "General Ethical Principles of Animal Experiments", adopted by the 5th National Congress on Bioethics (Kyiv, 2013), (Minutes No. 198 as of 21.10.2021 from the meeting of the Commission on Biomedical Ethics of the Poltava State Medical University (2010:276:0033:0079). Given that, according to the publications, microbiota is mainly concentrated in the caecum, we chose it as the object of study (Shevchenko *et al*., 2017; Shi *et al*., 2017; Hryn *et al*., 2018a,b).

The animals under ether anesthesia (Flecknell, 2016) (with observance of sterile conditions and relevant requirements for the ethics of experimental research on animals) alternately underwent incision of the peritoneal cavity along the linea alba.

Peritoneal cavity of animals was infected by perforating the anterior wall of the cecal apex at four sites using a G16 injection needle (Fig. 1).

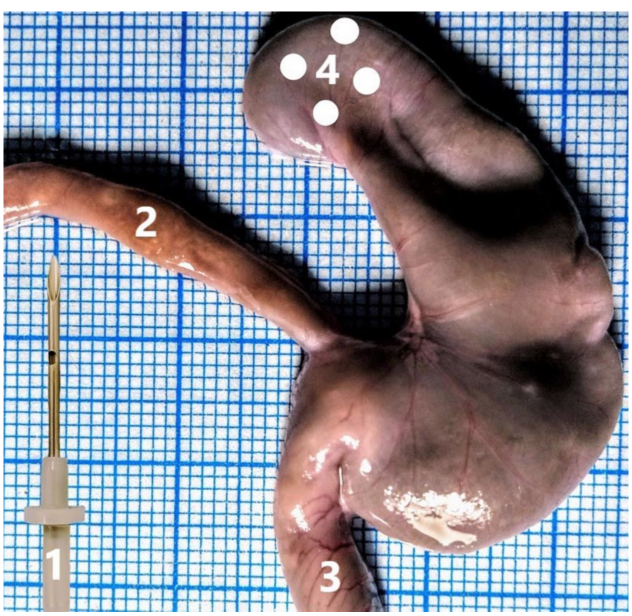

Fig. 1. The caecum of an albino rat with perforation sites. 1. a needle used for perforation of the wall of the caecum; 2. ileum; 3. colon; 4. the apex of the caecum.

After perforating the edge, the abdominal wall was sutured with a polypropylene thread that does not possess antigenic properties.

Vivisection of the animals was carried out by an overdose of ether anesthesia (Flecknell, 2016) for three days with an interval between three groups of animals (five subjects in each group) equal to 24 hours. It should be noted that during the experiment, which lasted 3 days, not a single animal died. At the same time, all animals during the first day were in a postoperative numbness, without showing any reaction to food and water. And only after some time, on the second day of the experiment, the animals began to recover from the operation, returning to their usual way of life.

After systematic and methodically correct vivisection, we proceeded with sequential opening their peritoneal cavity and immediately irrigated it with 10 % solution of neutral formalin, which ensured the preservation of all its organs in their vital state for the entire duration of the morphological study, which was carried out using traditional anatomical and histological methods. The obtained serial paraffin slices of 4 µm thick were stained with hematoxylin-eosin.

Specimens were studied and documented using the Konus light microscope equipped with the Sigeta DCM-900 9.0MP digital microphotographic attachment with the Biorex 3 software adapted for these studies (serial number 5604). Morphometric characteristics of the tissue structures of the corresponding specimens were obtained using a system for visual analysis of histological specimens, as well the Sigeta X 1 mm/100 Div.x0.01 mm object micrometer, the scale of which (equal to 1 mm, where the smallest division corresponds to 10 µm) was applied on the corresponding microimage obtained at an equivalent magnification. Statistical processing of the resulting data was carried out on a personal computer using the Prism 5 (version 5/03) and Microsoft Excel 2010 software packages, as well as methods of descriptive statistics and statistical analysis. Descriptive statistics are presented as mean ± standard error of the mean (M±m). Qualitative indicators were presented in the form of absolute values (n) and percentages (%).

The values of the studied parameters between the groups were compared using the Kruskal-Wallis test (One-Way ANOVA).

The differences were considered statistically significant at $p<0.05$.

RESULTS

Preliminary examination of the peritoneal cavity of all 15 animals showed that the regular stereotypical defense response to perforated damage to the caecum is the well-known omental tamponade (Platell *et al*., 2000). Interestingly, in the peritoneal cavity of mature male rat, unlike in human one, in addition to the greater omentum, two additional, homologous to it in structure, derivatives of the visceral peritoneum, which in the scientific literature we first called epididymal omenta, since they are related to the epididymides, have been found (Hryn *et al*., 2023a,b). Therefore, the findings of the detailed analysis have found that in the vast majority of cases, namely in 11 animals, the tamponade of the perforated wall of the caecum was made by the greater omentum (73.34 %) (Fig. 2 A, B), and in 4 animals it was made by one of the epididymal omenta (26.66 %) (Fig. 3).

The next task of our study was to find out how tight the omentum was adhered to the perforated wall of the caecum, since no data on this issue have been found in the literature. Consequently, the histological cross-sections of the tissue have been made. Importantly, the analysis of such histological sections aids in distinguishing the tissue structures that, on the one hand, belong to the intestinal wall, and on the other hand, to the corresponding omentum.

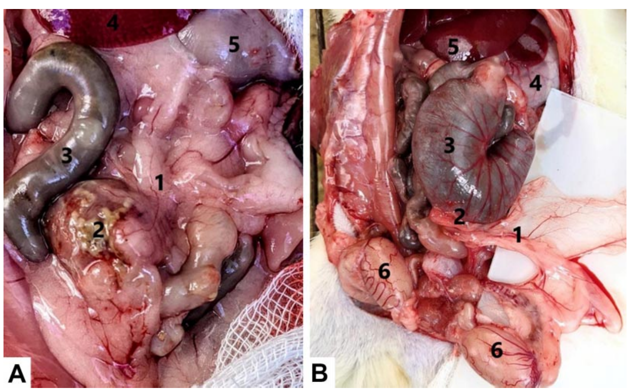

Fig. 2. Tamponade with the greater omentum (A) and epididymal omentum (B) of the perforated caecum of the male rat following one day of the experiment. Macroimage. A. 3 × magnification, B. 2 × magnification. A: 1. Greater omentum; 2. The site of consolidation of the greater omentum with the perforated caecum; 3. Colon; 4. Liver; 5. Stomach. B: 1. Epididymal omentum; 2. The site of consolidation of the epididymal omentum with the perforated caecum; 3. Caecum; 4. Stomach; 5. Liver; 6. Testicles.

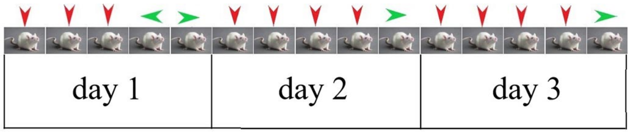

Fig. 3. Chronometric assignment of albino rats into groups with a marked involvement of the corresponding omentum in the tamponade of the perforated caecum (red arrows mark tamponade of the perforated caecum made with the greater omentum; green arrows mark tamponade of the perforated caecum made with the epididymal omenta (arrow to the left – with the left epididymal omentum, arrow to the right – with the right epididymal omentum). *Note: p=4,455

Figure 4 presents the microimage of one of the sections, obtained within 24 hours of the experiment

In the cross-section, the microimage clearly identifies the cecal mucosa and the muscular layer, closely adjacent to it inferiorly. In the mucous membrane, the epithelial layer is clearly identified, speckled with crypts, as well as the lamina propria with a defect in the center, resulted from the perforation of the caecum. Noteworthy, at the lower part of the microimage, where the omentum is presented, its adhesion to the intestinal wall occurs through the close contact between the two layers of mesothelial cells, which undergo reduction. Consequently, consolidation (or adhesion) occurs between the tissue structures of the omentum and the muscular layer of the caecum.

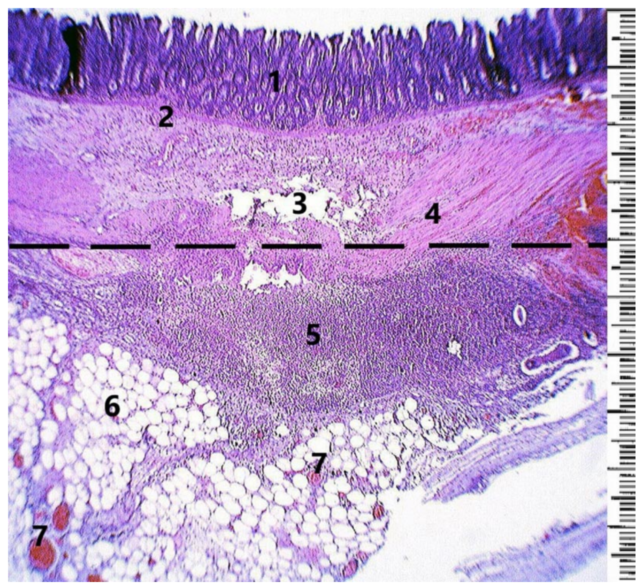

Fig. 4. The zone of consolidation between the greater omentum and the perforated wall of the caecum of a male rat after 24 hours of the experiment. Paraffine section; H & E stain. Objective lens 4 × magnification. The smallest division in the metric scale is 10 μm. 1. Epithelial layer of the mucous membrane of the caecum; 2. Lamina propria of the caecum; 3. Traces of perforated damage; 4 . Muscular layer of the caecum; 5. Lymphoid infiltrate; 6. Adipocytes of adipose tissue of the greater omentum; 7. Blood vessels. The dotted line marks the margin of consolidation between the omentum and the cecal wall.

Moreover, on the first day of the experiment, the phenomena related to the reaction of the omentum in response to pathogenic invasion was noted in the contact zone. It was manifested by the pronounced lymphoid infiltration at the site of its perforation, which was noted between the omentum and the lamina propria of the mucous membrane of the caecum (Fig. 4). At the same time, in its dense aggregation of lymphoid elements numerous plasma cells were detected, indicating the development of humoral immune response on the site of inflammation.

Thus, within the first day of the experiment, local reduction of pathogenic microflora and the development of humoral immunity response occurred in the area of perforation of the caecum with its tamponade with one or another omentum. Subsequently, we found that further prolongation of this process over the next 24 hours did not lead to any qualitatively new morphological transformations on the site of damage. Notably, all changes were limited to a more extensive proliferation of lymphoid infiltrations, accompanied by the invasion of blood microvessels into them (Fig. 5).

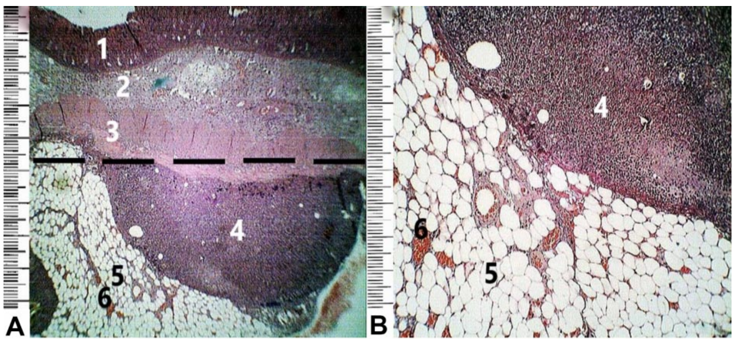

Fig. 5. The zone of consolidation between the epididymal omentum and the perforated wall of the caecum of a male rat following 2 days of the experiment. Paraffin section; H & E stain. A – objective lens 4 × magnification; B – objective lens 10 × magnification. The smallest division in the metric scale is 10 µm. 1. Epithelial layer of the mucous membrane of the caecum; 2. Lamina propria of the caecum; 3. Muscular layer of the caecum; 4. Lymphoid infiltrate; 5. Adipocytes of adipose tissue of the omentum; 6. Blood vessels. The dotted line marks the margin of consolidation between the omentum and the cecal wall.

At the same time, thickening of the adipose tissue of the omentum, which, thereby, isolates the peritoneal cavity from the foci of inflammation was noted.

At the end of the experiment, namely, following 3 days, in the zone of consolidation of the omentum with a perforated wall of the caecum, morphological signs of reorganization of lymphoid infiltrations in the form of two-row trajectories of immunocompetent cells was noted. At the same time, the degree of their vascularization was significantly increasing due to numerous hyperemic blood microvessels growing into them from the adipose tissue of the omentum.

It is noteworthy that in some cases in the adipose tissue of the omentum (in the zone of lymphoid infiltration) the formations similar in shape and cytoarchitectonics to mature lymphoid nodules resembling milk spots were found (Fig. 6).

DISCUSSION

The problem related to peritonitis, notwithstanding the enhancement of the methods of diagnosis and treatment, surgical technique, the achievements of anesthesiology and resuscitation and pharmacology, remains one of the most complex and relevant in emergency abdominal surgery to date (Ross *et al*., 2018; Ouf *et al*., 2020). The high rates of mortality in postoperative diffuse purulent peritonitis encourages authors to develop novel methods for modeling septic peritonitis (Ness *et al*., 2003; Mascena *et al*., 2018). The main condition for modeling peritonitis is the reproducibility and uniformity of its development, which significantly affects the results of an experimental study (Witteveen *et al*., 2016).

Currently, the diverse experimental models of peritonitis exist, and all of them have their advantages and disadvantages. The common models of peritonitis can be the methods of introduction of foreign bodies (Hryn *et al*., 2023a) or chemicals into the abdominal cavity, or bacterial contamination of the abdominal cavity with cultures of pathogenic microorganisms, or by opening the lumen of the colon or combination of both methods (Fantin *et al*., 2019; Montenegro *et al*., 2020; Vintrych *et al*., 2022).

Among the models reproduced by surgical intervention, the method proposed by O`Donnell Jr. *et al.* (1975), is noteworthy. The caecum of experimental animals (dogs) was ligated. At the same time, necrosis of the dome of the caecum occurs simultaneously with the formation of intestinal obstruction, which leads to the development of enteric dysfunction, resulted in peritonitis. The study showed that the animals had the signs of intoxication following 24 hours after the surgery (O'Donnell Jr. *et al*., 1975).

Fig. 6. The zone of consolidation between the greater omentum and the perforated wall of the caecum of a male rat at the end of day 3 of the experiment. Paraffin section; H&E stain. Objective lens 4 × magnification. The smallest division in the metric scale is 10 µm. 1. Epithelial layer of the mucous membrane of the caecum; 2. Lamina propria of the caecum; 3. Lymphoid infiltrate; 4. Adipose tissue of the greater omentum.

Given the shortcomings of the method, Wichterman *et al*. (1980), described a model of suture of the cecum with a ligature followed by perforation of the latter with 18 G and 22 G cannulas. The cecum is ligated distally to the ileocecal valve and perforated by punctures with an injection needle.

Some authors suggested to supplement the model of Wichterman *et al*. (1980), with mandatory resection of the greater omentum due to its functional features. To create a model of peritonitis, perforations were made in the avascular zone of the dome of the caecum in 6–8 sites on different sides of the intestine, followed by the resection of the greater omentum. The authors hypothesize that the slow, permanent flow of the intestinal contents to the abdominal cavity avoids the development of infectious and toxic shock (Göl Serin *et al*., 2019; Liu *et al*., 2021).

The use of models with damage to the intestinal wall induce the development of peritonitis, brings the process closer to real pathogenetic changes in the abdominal cavity in case of postoperative peritonitis (Murando *et al*., 2019; Capcha *et al*., 2021; Utiger *et al*., 2021). However, the disadvantages of these methods include the uncontrolled volume of intestinal contents entering the abdominal cavity. In the case of its significant entering, there is a high probability for developing abdominal sepsis and death of animals during 24 hours of the experimental study (Murando *et al*., 2019).

Experimental modeling using the surgery, especially with perforation of the wall of the caecum, can limit the purulent process (Wichterman *et al*., 1980; Utiger *et al*., 2021). It is known that one of the main factors that determines the course of the postoperative period in acute surgical pathology of the abdominal organs is the involvement of the greater omentum in the formation of the intraperitoneal inflammatory focus. The greater omentum demarcates the intraperitoneal focus of inflammation, forming infiltrative-adhesive processes, which can prevent the rapid spread of infection to other parts of the abdominal cavity (Platell *et al*., 2000; Iizuka *et al*., 2021). The greater omentum is a barrier to bacterial invasion and, as a result, can convert the source of a possible development of peritonitis into a local abscess (Di Nicola, 2019; Liu *et al*., 2021).

However, the data presented in our publication on the consolidation of the greater omentum and serous formations of the epididymides, completely homologous to the latter (Hryn *et al*., 2022; Hryn *et al*., 2023b), with the perforated openings of the cecum have not been found in the scientific literature, as well as the morphological aspects of the local immune response to infection of the peritoneal cavity of the experimental animals.

CONCLUSIONS

1. Perforative damage to the wall of the caecum of albino male rats is eliminated most often (in 73.34 % of cases) by its tamponade with the greater omentum. In other cases, this role is performed by one of its epididymal homologues (26.66 %) p=4,455.
2. The initial, fundamental stage of tamponade of the perforated caecum with one or another omentum, occurred within the first days of the experiment, is a tight interstitial consolidation between them, as well as the invasion of blood vessels to the site of infection, which ensure the delivery of the appropriate immunocompetent clones to the site of infection cells. The result of this process is the formation of extensive lymphoid infiltrates in this zone.
3. Prolongation of this process, observed at the end of the second day of the experiment, is manifested mainly by the quantitative multiplication of the above tissue structures. At the same time, with an increase in the vascularization of this structural complex, a noticeable growth of adipose tissue occurs in it.
4. Qualitatively new morphological transformations in the damage zone were noted at the end of the third day of the experiment. Basically, they are manifested by the reorganization of lymphoid infiltrates and their transformation into mature lymphoid nodules (milky spots) of a new generation. At the same time, in the zone of the inflammatory process, proliferation of adipose tissue occurs, which isolates this inflammatory focus from the peritoneal cavity with a thick layer.

This, in our opinion, can explain the fact that during the experiment, which lasted 3 days, not a single animal died, and successfully recovered thereafter.

HRYN, V. & MAKSYMENKO, O. Características morfológicas de los resultados del modelado experimental de peritonitis séptica. *Int. J. Morphol., 42(2)*:446-451, 2024.

RESUMEN: Las investigaciones experimentales dedicadas al estudio de los mecanismos de patogénesis de la peritonitis aguda y el desarrollo de nuevos métodos de tratamiento médico y quirúrgico son cada vez más relevantes. Hoy en día, la medicina experimental conoce muchas formas diferentes de modelar la peritonitis séptica y eliminarla, pero se subestima el papel del sistema inmunológico local, mientras que él participa directamente en la inflamación. El objetivo de nuestro trabajo fue estudiar las características morfológicas de los resultados del modelado experimental de peritonitis séptica en ratas blancas. El estudio incluyó 15 ratas macho blancas, sexualmente maduras que pesaban 276,75 ± 6,56 gramos. Se realizó una simulación de peritonitis séptica perforando la parte superior del ciego con cuatro punciones con una aguja de inyección G16. Como resultado del experimento, después del examen de la cavidad peritoneal, a los 15 animales se les diagnosticó taponamiento del omento o lesión perforada del ciego. En 11 casos, la pared perforada del ciego fue recubierta por el omento mayor (73,34 %), y en los otros 4 animales el taponamiento se realizó por uno de los

epidídimos (26,66 %). La etapa inicial del taponamiento con omento mayor o epidídimo de un ciego perforado comienza el primer día del experimento y consiste en una estrecha consolidación intersticial entre ellos, así como en la invasión de los vasos sanguíneos desde el lado del omento hasta el foco de infección, que aseguran la entrega de las células inmunocompetentes apropiadas. Como resultado de este proceso, se forman intensos infiltrados linfoides en esta zona, así como el crecimiento de tejido adiposo, que aísla el foco inflamatorio de la cavidad peritoneal con una gruesa capa.

PALABRAS CLAVE: Peritonitis; Omento mayor; Duodeno; Estómago; Ciego; Testículo; Linfonodo; Nódulo linfático; Adipocitos; Células inmunocompetentes.

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