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Pathohistological features of Clostridium difficile-associated pseudomembranous colitis in post-COVID-19 patients

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ABSTRACT *AIM: to assess features of pathomorphological changes in the intestinal wall in patients who had new coronavirus infection SARS-CoV-2.*

PATIENTS AND METHODS: the study included 8 patients who underwent surgery for complications of pseudomembranous colitis and had previously COVID-19. Six patients underwent colectomy, and two underwent subtotal colectomy with end ileostomy. Histology of the removed specimens was standard.

RESULTS: in all specimens, in addition to the changes peculiar for pseudomembranous colitis, vascular lesions of the bowel wall were detected as vasculitis of small arteries and vessels of the microcirculatory network, phlebitis and thrombosis of venous vessels like in COVID-19. These pathological changes in blood vessels may reveal the intramural perfusion disorders of blood circulation, leading subsequently to ischemic changes.

CONCLUSION: when treating patients with pseudomembranous colitis and postcovid syndrome, it is necessary to take into account the mutually aggravating effect of both diseases, when assessing risks, determining indications for surgery and conservative measures.

KEYWORDS: *pseudomembranous colitis, Clostridium difficile, COVID-18, vasculitis, intestinal wall vein thrombosis*

CONFLICT OF INTERESTS: *the authors declare no conflict of interests*

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The new coronavirus infection COVID-19 is often accompanied by complications from the digestive tract [1–3]. The rate of these complications is explained by the presence of ACE-2 receptors in the abdominal organs [4].

According to the literature, 18.9% of patients with COVID-19 have gastrointestinal complications [5], which occur in severe form in one quarter of patients with COVID-19, including 0.5% of cases with acute inflammation of the large intestine [11]. Among gastrointestinal complications, pseudomembranous colitis (PMC) occupies a special place, accompanied by severe diarrhea, intoxication, symptoms of "acute abdominal pain", fever, and leukocytosis, which usually occurs after antibiotic therapy for SARS-CoV-2 (antibiotic-associated PMC — AAPMC). It is known that AAPMC is most often found in surgical units and, especially, in patients after bowel surgery [5]. As a rule, PMC is a Clostridium difficile-associated disease that develops when the intestinal microbiota is disrupted with excessive colonization of Cl.difficile, whose toxins cause inflammation and damage to the large intestine [6–9]. Cl.difficile (CD) bacteria belong to the group of obligate anaerobes, the most important factors of their pathogenicity are enterotoxin A and cytotoxin B [12].

A characteristic feature of this lesion is fibrinous overlays on the mucous layer of the large intestine [10].

Along with taking antibiotics, the development of PMC may be caused by surgeries on the organs of the digestive tract, diseases and injuries leading to circulatory disorders and ischemia of internal organs [13].

PMC was first described by Finney, J.M. in a 22-year-old patient on the 10th day after gastric surgery, who developed severe bloody diarrhea, which led to death [14]. The pathological study of changes in the intestine was described as “diphtheria colitis” due to the presence of fibrinous overlays on the surface of the mucosal lesions.

If laboratory tests for Cl.difficile infection are negative with a characteristic endoscopic picture, then other, less common causes should be sought for to make a correct diagnosis — ischemic colitis, nonspecific intestinal inflammation (ulcerative colitis), medications, chemicals, vasculitis, etc. [15].

In addition to CD infection, oral antibiotics, colonization of the large intestine mucosa, production of exotoxins, and individual risk factors such as age, previous illnesses are important for the development of PMC [12]. CD is diagnosed based on the characteristic symptoms and the detection of toxins or bacteria in the feces of patients [16–18]. Conservative treatment of PMC includes the use of vancomycin and metronidazole at a dose of 500 mg every 6 hours [19,20]. In some cases, surgical decompression of the intestine and direct administration of vancomycin or metronidazole through a colostomy may be preferable in patients with severe intestinal pathology [19].

With the development of complications such as toxic megacolon or intestinal perforation, surgery is a life-saving procedure. The incidence of necessary surgeries in patients with Cl.Difficile-associated diseases is 0.39–3.6%. Indications for surgery are: persistence or progression of symptoms of intoxication, continuous diarrhea, symptoms of peritonitis or intestinal perforation, increased changes in the large intestine, confirmed by repeated CT. In these cases, ileo-cecostomy or decompressive colostomy are performed. Subtotal or total colectomy is the surgery of choice in patients with fulminant toxic megacolon [21]. Mortality in case of PMC requiring surgical treatment ranges from 30% to 50%.

AIM

To find features of pathomorphological changes in the intestinal wall by histology of removed specimens for pseudomembranous colitis in patients who have suffered a new coronavirus infection SARS-CoV-2.

PATIENTS AND METHODS

Removed specimens of 8 patients with PMC who had COVID-19 before the PMC, underwent surgery for complications of PMC: toxic megacolon (n = 4), peritonitis without perforation of the colon (n = 2), perforation of the colon (n = 2) for the period from September 2020 to March 2022.

The mean age of the patients was 57.5 ± 8.7 years, including 5 women and 3 men. All patients suffered from COVID-19 in severe (5) or moderate-severe forms (3), and were hospitalized in covid-hospitals, with 3 patients undergoing mechanical ventilation for up to 7–10 days. Due to pneumonia, all patients received 2–3 antibiotics, glucocorticoids, and 5-monoclonal antibodies. Six patients underwent colectomy, including two patients with resection of up to 40 cm of the ileum due to severe inflammatory changes with ileostomy, and two more patients underwent subtotal colectomy with ileostomy.

The diagnosis of PMC was suspected based on the clinical picture (abdominal pain, diarrhea, fever), laboratory data (leukocytosis > 15 × 10^9/l, CRP > 50 mmol/l) and confirmed by colonoscopy, CT, and stools for toxin A and B Cl.difficile.

In all cases, the diagnosis was confirmed, and toxins A and B were identified in 5 cases. Video laparoscopy was performed not only as a diagnostic procedure, but also as a therapeutic procedure, but in all cases, due to pronounced dilation and destructive changes in the colon, laparotomy was performed.

For histology, pieces from various parts of the colon and ileum were fixed in 10% neutral buffered formalin. After histological processing of the samples, slices of the intestinal wall were made, followed by staining with hematoxylin and eosin.

RESULTS

Pathomorphological changes characteristic of PMC — inflammatory exudate in the form of a pseudo-membrane over the affected areas of the large intestine mucosa with punctate necrosis of the surface crypts were detected during the examination of biopsy material taken during colonoscopy and surgical samples. When PMC complications occurred in the form of toxic megacolon, peritonitis, and perforation of the colon, these pathomorphological changes were significantly more pronounced, spread to deeper layers of the large intestine wall, and involved the terminal part of the ileum (Fig. 1,2).

Figure 1 shows a micro-specimen of the ileum: the bottom of an ulcer with granulation tissue, represented by a multitude of thin–walled vessels with an abundance of cellular elements around, with neutrophils dominating in one field of view, and mononuclears — in the other.

The pathohistological picture in the wall of the small intestine adjacent to the ulcer is shown in Figure 2: in the center of the specimen is an intermuscular capillary net, blood vessels are anemic with a flattened endothelium with signs of capillaritis, moderate swelling of the intermuscular layers is observed, inflammatory infiltrate is abundant and is represented by lymphoplasmocytic elements. Proliferation and productive vasculitis in the microcirculatory bed are noted.

The manifestations of productive vasculitis in the intermuscular area of the ulcerative lesion of the colon are demonstrated by a micro-specimen in Figure 3. On high magnification in the center of the arteriole, the wall thickens due to edema and cell proliferation of the lymphoplasmocyte series, the basement layer is preserved with foci of endothelial proliferation in the form of a focal cluster, the endothelium with hyperchromic nuclei, uneven subendothelial edema is noted. Near the ulcerative defect of the colon, in a destructively altered area of the intestine, a venous vessel is in the center of the visual field; inflammatory infiltration is in the perivascular space; the lumen of the vein is completely blocked by a mixed thrombus consisting of fibrin, erythrocytes and decaying leukocytes; the intestinal wall is uneven in thickness and in a state of necrosis; the endothelium is necrotized over a large area; it is difficult to differentiate the remaining cellular elements (necrotic thrombovasculitis) (Fig. 4). Pronounced changes in the microcirculatory bed are shown in Fig. 5: microcirculation vessels in a state of fullness, with the phenomena of focal marginal standing of neutrophils, inflammatory infiltration in the intercapillary space, represented by lymphoid and plasma cells. These pathomorphological changes can be regarded as chronic immune

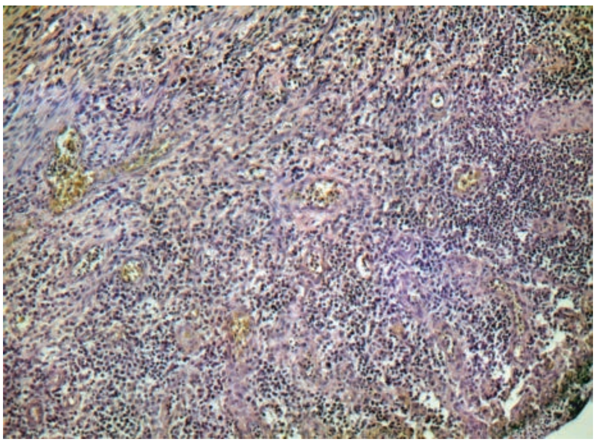

Figure 1. *The bottom of the ulcer of the small intestine. Magnification ×100. Ocd.: hematoxylin and eosin*

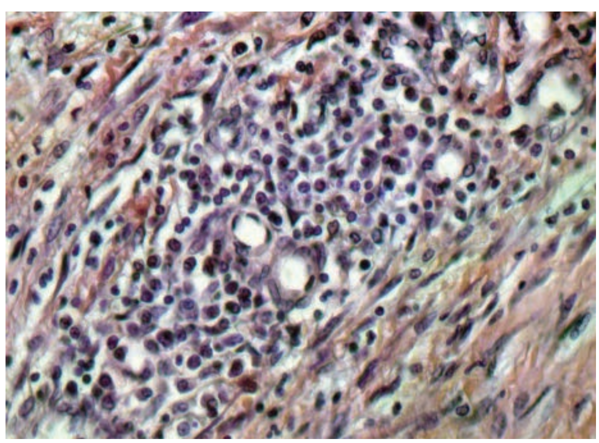

Figure 2. *The nearby area to the ulcer of the small intestine. Magnification ×400. Ocd.: hematoxylin and eosin*

lesion, i.e. capillaritis (rather, associated with SARS-Cov-2).

The spectrum of pathomorphological changes in the large intestine is quite diverse, including from superficial erosive to deep ulcerative, deep ischemic lesions of the large intestine. So, Fig. 6 shows the area of erosive changes in the mucous layer of the colon, with its superficial necrosis, acute inflammatory infiltration covering the mucosa and the adjacent submucosal layer. On another micro-specimen (Fig. 7) there is a fragment of the colon with an ulcerative defect of the mucous layer, the bottom and edges of the ulcer are represented by granulation tissue diffusely infiltrated by inflammatory cellular elements; in the field of view small and minute full-blooded vessels, fields of edematous tissue are visible. The destruction of the mucous layer is combined with the phenomena of incomplete regeneration, which is clearly visible in the upper left area of the specimen. There is pronounced edema with protein impregnation in the submucosal layer, the vessels are full-blooded and dilated. The following specimen demonstrates damage to the veins with the development of phlebitis in the colon wall (Fig. 8): a vein of a fairly large caliber, its wall is infiltrated by neutrophilic leukocytes with lesion of the endothelium, which is absent over a large area, inflammatory changes spread prevascularly to the intermuscular space.

Pronounced changes were detected in the submucosal layer of the colon, where the main vascular net of the intestinal wall is located. Figure 9 shows a micro-specimen of a fragment of the submucosal layer of the colon: edematous stroma, diffuse inflammatory infiltration, many different-sized

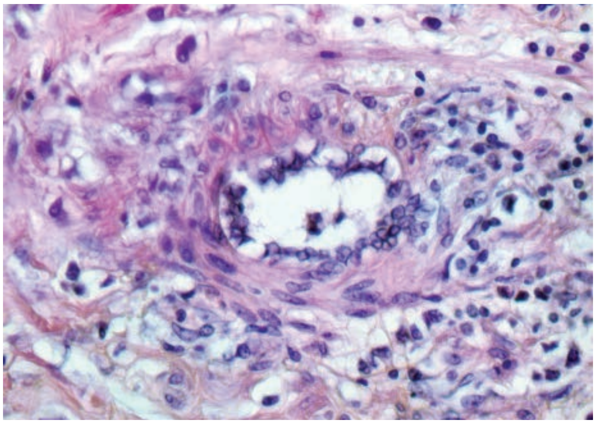

Figure 3. *Productive vasculitis of the intermuscular zone of the ulcerative defect of the colon. Magnification ×400. Ocd.: hematoxylin and eosin*

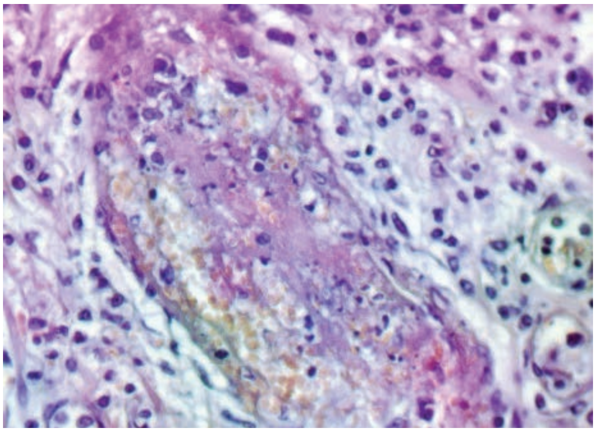

Figure 4. *Destructively altered area of the colon near the ulcerative defect. Magnification ×400. Ocd.: hematoxylin and eosin*

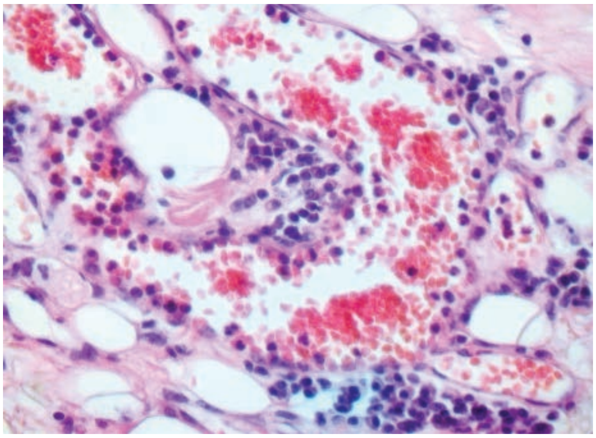

Figure 5. *Microcirculation of the colon wall. Magnification ×400. Ocd.: hematoxylin and eosin*

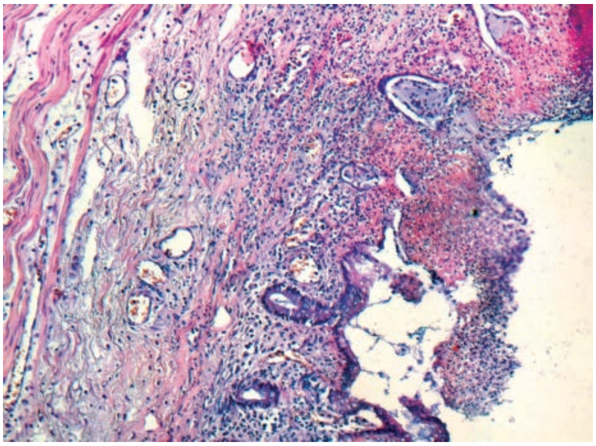

Figure 6. *The area of erosivechanges in the mucousmembrane of the colon. Magnification ×100. Ocd.: hematoxylin and eosin*

vessels are determined, a micro-vessel with fibrinoid necrosis of its wall is presented in the center of the specimen in a longitudinal section, and in adjacent areas granulations with plasma cells, lymphocytes and monocyte-macrophage cells are largely indicative of immune inflammation (probably as a manifestation of the post-covid syndrome). The autonomic nervous system of the intestine is also involved in the pathological process, which is confirmed by the micro-specimen in Figure 10: on a fragment of the muscular layer of the colon, an intermuscular nerve ganglion is represented, with dystrophic changes in nerve cells, signs of karyopycnosis and karyolysis in individual cells, pronounced cellular infiltration along the periphery of the ganglion, which is dominated by lymphoid elements, vessels of the microcirculatory bed are full-blooded.

DISCUSSION

COVID-19 can lead to thrombotic complications in both the venous and arterial systems due to severe inflammation, platelet activation, endothelial dysfunction, and stasis [22].

The prevalence of venous thromboembolic complications among patients hospitalized with COVID-19 can reach 37% [23], arterial complications — from 1% to 18% [23]; and the incidence of these complications was higher in patients hospitalized in intensive care units [23,24]. Many of the factors associated with the patient (old age, male gender, hypertension, diabetes, obesity) predispose the general population to the development of thromboembolic complications [25,26].

In a study of 909,473 patients with COVID-19 and 32,429 patients hospitalized with COVID-19, the

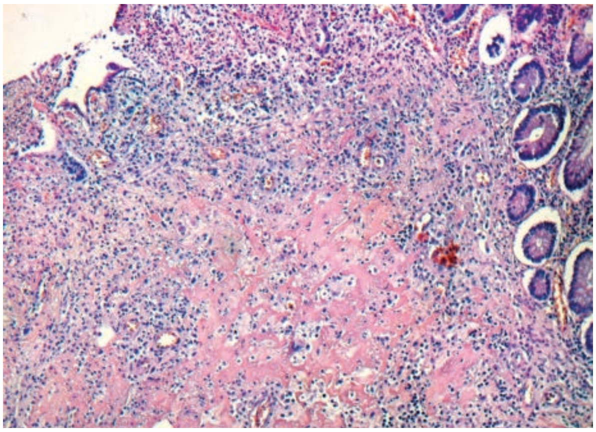

Figure 7. *Fragment of the colon with ulcerative defect of the mucous membrane. Magnification ×100. Ocd.: hematoxylin and eosin*

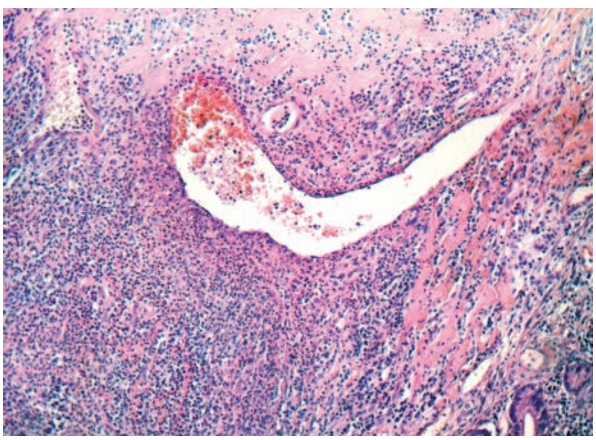

Figure 8. *Phlebitis of the colon wall. Magnification ×100. Ocd.: hematoxylin and eosin*

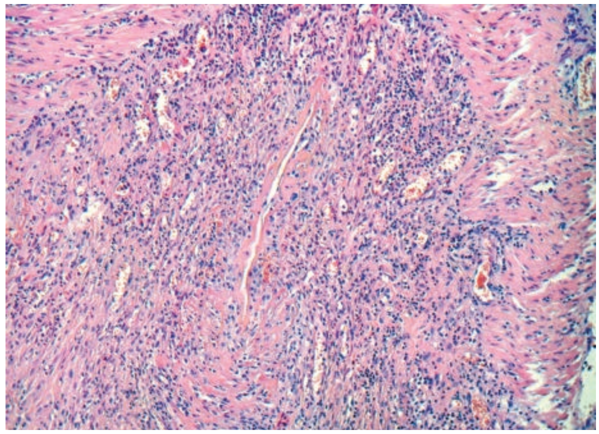

Figure 9. *Fragment of the submucosal layer of the colon. Magnification ×100. Ocd.: hematoxylin and eosin*

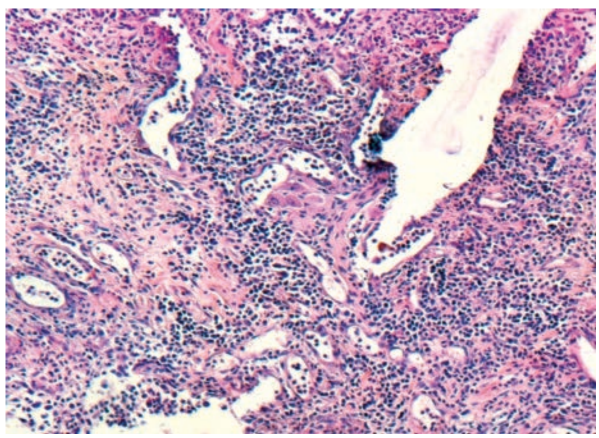

Figure 10. *A fragment of the muscular lining of the colon. Magnification ×120. Ocd.: hematoxylin and eosin*

cumulative 90-day incidence of venous thromboembolism ranged from 0.2% to 0.8% among COVID-19 patients and up to 4.5% among those hospitalized, arterial thromboembolism — 0.1% — 0.8% and 3.1%, respectively, mortality varied from 1.1% to 2.0% among patients with COVID-19 and up to 14.6% among hospitalized patients [27].

PMC is morphologically defined as "acute colitis" with inflammatory exudate (pseudo-membrane) above the areas of lesion on the mucous layer [28]. Fibrinous-purulent exudate forms mushroom-like protrusions on the surface of the mucous layer, the surface crypts show punctate necrosis and expansion. In the later stages, all crypts become necrotic and the histological picture resembles ischemic colitis. The surface sections of its own plate are infiltrated by neutrophils; fibrin thrombi are detected in some capillaries.

CD toxins A and B inside intestinal mucosal cells cause glycosylation of proteins involved in signaling and regulatory processes, which is accompanied by cell destruction, cytokine activation, and eventually cell death [15]. In addition, contacts between large intestine cells are disrupted, which promotes neutrophil infiltration, causing an inflammatory reaction characteristic of colitis [29]. In the process of inflammation, further activation of the immune system occurs, the release of proinflammatory cytokines (IL-1, IL-8, tumor necrosis factor, leukotriene-B4), which leads to the formation of focal micro-abscesses, pseudo-membranes consisting of fibrin and cellular elements of inflammation [15]. During colonoscopy, pseudomembranes on the surface of the mucous layer of the large intestine have the appearance of characteristic raised yellow-white nodules or plaques. Most often, PMC has to be differentiated from ischemic colitis, the typical localization of which is the sigmoid colon and its characteristic distinguishing feature is the hyalination of its own plate [30], and atrophy of the mucous layer with rare pseudo-membranes and pseudo-polyps is observed with more severe ischemia [31]. Chronic ischemic colitis is characterized by a preserved crypt architecture, a mixed inflammatory infiltrate spreading to its own plate, and collagen deposition in the form of streaks or uneven distribution under the epithelium [32]. Similarly, nonspecific inflammatory bowel diseases (ulcerative colitis, Crohn's disease) are characterized by the presence of lymphoplasmocytosis, cryptitis, and crypt abscess.

Cytomegalovirus colitis is a common manifestation of this viral infection, histologically characterized by large basophilic bodies, inclusions in the nuclei ("owl eye") along with ischemic ulcers. The mechanism of pseudo-membrane formation is not clear, although poor tissue perfusion and anoxia similar to ischemic colitis are assumed [33].

Pathological signs of enterocolitis caused by Staphylococcus aureus are characterized by the presence of pseudo-membranes and fibrin, necrotic areas with polymorphonuclear cells and clusters of gram-positive cocci, sometimes with necrosis of the intestinal wall [34].

CONCLUSION

The removed specimens of the intestine after operation — colectomy and subtotal resection of the colon in patients with pseudomembranous colitis after they suffered from the new coronavirus infection COVID-19 — indicate a complex mechanism of development of this complication. In addition to inflammatory changes in the intestinal wall caused by Clostridium difficile and toxins A and B, vascular lesion of the wall in the form of vasculitis with lesion of small arteries and vessels of the microcirculatory bed, phlebitis and thrombosis of venous vessels is important. These pathological changes in blood vessels can be a determining factor in the development of perfusion disorders of blood circulation, leading subsequently to ischemic changes and the development of perforation of the intestinal wall, peritonitis, acute toxic dilatation of the colon. Severe lesion of the autonomic nervous system of the intestine, the ganglion cells of the Averbach and Meissner nerve plexuses, can undoubtedly play an important role in the mechanism of development of the latter. Many manifesting clinical symptoms in the form of PMC, the development of surgical complications from the intestine, should be considered as consequences of COVID-19 treatment (antibiotic therapy), and as a manifestation of post-covid syndrome with the development of autoimmune vasculitis and thrombotic complications characteristic of SARS-CoV-2.

The authors believe that in the treatment of patients with PMC and post-covid syndrome, these pathological mechanisms should be taken into account for their drug correction.

AUTHORS CONTRIBUTION

Concept and design of the study: *Vil' M. Timerbulatov, Makhmud V. Timerbulatov*

Collection and processing of the material: *Sergey V. Shchekin, Ruslan R. Garaev, Tagir I. Mustafin*

Statistical processing: *Shamil' V. Timerbulatov, Aigul R. Gafarova*

Writing of the text: *Vil' M. Timerbulatov, Aigul R. Gafarova*

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