Case Report

https://doi.org/10.23934/2223-9022-2021-10-3-469-476

A Multidisciplinary Approach to the Treatment of COVID-Associated Complications after Pancreatoduodenal Resection (Case Report)

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ABSTRACT We report a clinical case of treatment of a complicated postoperative course in a patient who underwent pancreatoduodenal resection associated with coronavirus infection. Prevention and treatment of such complications have been suggested.

Pancreatoduodenal resection (PDR) is indicated for malignant tumors of the pancreatic head, duodenum or its large papilla, distal common bile duct, as well as in chronic pancreatitis with a predominant lesion of the pancreatic head with severe pain syndrome.

The given clinical observation describes an example of treatment of a patient who developed a series of thromboembolic complications in the early stages after PDR performed for a neuroendocrine tumor of the pancreatic head. The oncology disease, extensive surgery such as PDR, and the postoperative period itself are risk factors for the development of various thromboembolic complications. According to the literature, the incidence of thromboembolic complications after PDR is 3–3.3%.

The reason for the atypical course of the postoperative period when performing pancreatoduodenal resection in patients with tumor of the pancreas may be conditions that are not directly related to either the pathology of the pancreas or the features of the surgical intervention. When analyzing the patient's condition, one should take into account the conditions of treatment. In such situations, proper detection of COVID-19 and adequate correction of therapy can fundamentally change the outcome of the disease.

Keywords: pancreas, pancreatoduodenal resection, coronavirus infection (COVID-19)

For citation Kim TE, Lebedev DA, Magomedbekov MM, Nugumanova KA, Petrikov SS, Popugayev KA, et al. A Multidisciplinary Approach to the Treatment of COVID-Associated Complications After Pancreatoduodenal Resection (Case Report). *Russian Sklifosovsky Journal of Emergency Medical Care*. 2021;10(3):469–476. DOI: 10.23934/2223-9022-2021-10-3-469-476 (In Russian)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study was conducted without sponsorship

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BP – blood pressure
DPG – dopplerography
Du – duodenum
CT – computed tomography
INR – international normalized ratio
ICU – department of reanimation and intensive care
PDR – pancreatoduodenal resection
PH – pancreatic head
Pn – pancreas
PCR – polymerase chain reaction
RAS – renin-angiotensin system
PE – pulmonary embolism
USG – ultrasound examination
FFP – fresh frozen plasma

INTRODUCTION

Pancreatoduodenal resection (PDR) is indicated for malignant tumors of the pancreatic head (PH), duodenum (Du) or its large papilla, distal common bile duct, as well as in chronic pancreatitis with a predominant lesion of the pancreatic head with a pronounced painful syndrome. PDR involves the removal of the PH with the uncinate process, the distal common bile duct and Du. According to the standard adopted by European specialists, the radicalism of the operation is determined by the volume of removal of the affected organ and the surrounding lymphatic collectors [1].

PDR is considered the most serious intervention in pancreatic surgery, including resection and reconstructive stages. In specialized centers, the mortality rate is 1–5%, but the frequency of postoperative complications requiring endoscopic, minimally invasive and (or) surgical correction remains at the level of 20–40%. This leads to a delay in adjuvant chemotherapy and negatively affects the overall survival rate [2]. The technique of PDR is constantly being improved, but in most clinics of the world, the operation is performed in two main versions: in the form of the "classical" *Whipple* procedure with gastric resection and in the pyloric-preserving version of the *Traverso-Longmire* type of operation with the intersection of the duodenum 2-4 cm below the pylorus [3].

However, after PDR, a number of complications can arise: among the cohort of our patients, the largest proportion of early postoperative complications falls on postoperative pancreatitis - 15 patients (21.1%), failure of various types of anastomoses - 14 (20%) and formation of pancreatic fistulas - 14 (20 %). Bile leakage occurred in 8.5% of cases. Intra-abdominal bleeding and bleeding into the intestinal lumen were noted in 8.5% of cases. Gastrostasis as a complication of pancreas head resection occurs in about 30% of patients. Pneumonia - in 9 (8.5%). Thromboembolism of small branches of the pulmonary artery - in 3 (2.8%) [4]. The use of minimally invasive interventions allows to adequately eliminate postoperative complications without resorting to reoperation in a significant number of operated patients [4].

Given the *COVID*-19 pandemic, the likelihood of contracting coronavirus infection in patients who have undergone to PDR in the postoperative period against the background of a weakened immunity is high.

Clinical manifestations of coronavirus infection include possible complications from all organs and systems. The disease can take on a variety of forms, from asymptomatic carriage to life-threatening, fatal conditions. At the moment the following clinical variants of the course of *COVID*-19 can be distinguished: cardiovascular, respiratory, intestinal, renal, hepatic, diabetic, thromboembolic, microangiopathic, septic, cutaneous one [6].

An important role in the pathogenesis of infection is played by the body's hyperimmune response, which leads to diffuse alveolar damage, damage to the microvasculature and coagulopathy, which will subsequently cause thrombosis, including generalized, and thromboembolism [7]. It is possible to develop both *SARS-CoV*-2-associated endotheliitis with pulmonary vascular thrombosis and pulmonary embolism (PE), which is also characteristic of *COVID*-19. Thromboses of arteries of various organs with the development of their infarctions (myocardium, brain, intestines, kidneys, spleen) are described, there are descriptions of gangrene of the extremities too [8].

Case report

Patient L., 47 years old, applied to the N.V. Sklifosovsky Research Institute for Emergency Medicine in a planned manner in connection with the volumetric formation of the pancreas head with dimensions of 53x55x75 mm revealed during outpatient ultrasound examination (USG), extending to the isthmus, compressing the duodenum and the superior mesenteric vein. Tumor markers (cancer-embryonic antigen - CEA, angiotensin-converting enzyme - ACE, cancer antigen - CA 19-9) within normal limits.

Complaints upon admission for nausea, pain in the upper abdomen.

On examination, the patient's condition was satisfactory. Pulse 78 beats per minute, arterial pressure (BP) 130/85 mm Hg. The abdomen was not distended, painless on palpation. Peritoneal symptoms were negative. Urination without features.

Ultrasound confirmed the presence of a volumetric formation of the pancreatic head 92x62 mm, expansion of the Wirsung duct up to 30 mm, the common bile duct was not dilated, its diameter was 0.4 cm (Fig. 1).

Fig. 1. Ultrasound examination of the abdominal organs — mass lesion of the pancreatic head, dilated main pancreatic duct

Computed tomography (CT) of the abdominal cavity was performed, which confirmed the presence of a volumetric formation of the pancreas head 66x61x81 mm, unevenly accumulating contrast, which intimately adjoined the portal vein, squeezed the duodenal bulb, the main pancreatic duct was expanded to 30 mm (Fig. 2)

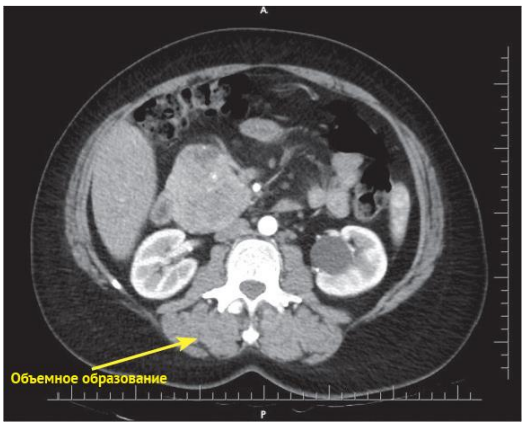


Fig. 2. Computed tomography of the abdominal organs with intravenous contrast enhancement — mass lesion of the pancreatic head

On esophagogastroduodenoscopy - the lumen of the duodenal bulb was deformed and narrowed to 1/2 due to pushing from the outside along the posterior semicircle (Fig. 3)

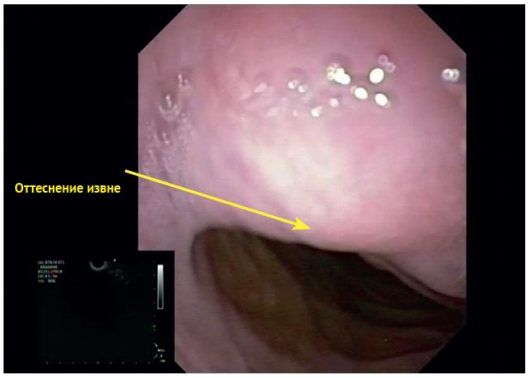


Fig. 3. Esophagogastroduodenoscopy — narrowing of the lumen of the duodenum

After examination, a preliminary diagnosis was established: chronic pseudotumorous pancreatitis with a predominant lesion of the pancreas head.

Considering the size of the formation, compression of the duodenum with partial duodenal obstruction, indications for a planned operation were established.

The patient was operated on 3 days after admission to the Institute: an upper-mid-median laparotomy was performed. During revision, there was no free fluid in the abdominal cavity. The expansion of the common bile duct up to 20 mm, an increase in the head of the pancreas up to 80x70 mm due to the volumetric formation of a densely knobby consistency, squeezing the Du were revealed. In other organs of the abdominal cavity and retroperitoneal space, no pathology was revealed. Intraoperative diagnosis: pancreatic tumor.

Cholecystectomy, pyloric-preserving pancreatoduodenal resection, formation of “end-to-loop” pancreatoenterogastroanastomosis, “end-to-side” choledochoenteroanastomosis, “end-to-side” enteroentero-anastomosis according to the method of Prof. V.I. Onopriev, drainage of the abdominal cavity were performed (Fig. 4-7).

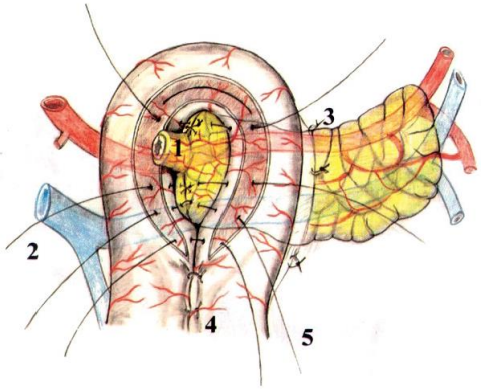


Fig. 4. Scheme of the formation of the end-to-loop pancreatoenteroanastomosis. 1 — main pancreatic duct stump; 2 — sutures on a section of pancreatic tissue are performed in the submucosal layer of the posterior intestinal wall; 3 — traction sutures in the peritoneum and parapancreatic tissue, fixing the pancreatic stump, are performed along the margin of the mesentery of the intestine and tied; 4 — the closing row of sutures of the mesentery and intestinal wall; 5 — serous-muscular sutures of the posterior wall of the jejunum.

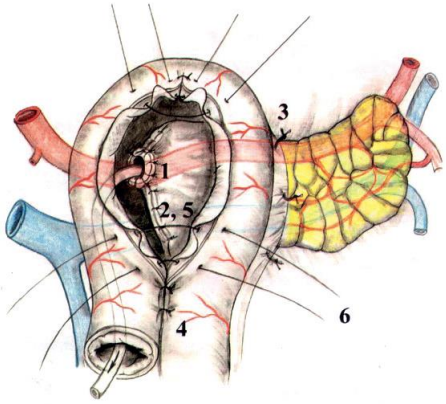


Fig. 5. Scheme of the formation of the end-to-loop pancreatoenteroanastomosis. 1 — main pancreatic duct stump; 2 — the sutures on the pancreatic tissue section are performed in the submucosal layer of the posterior intestinal wall and tied; 3 — traction sutures in the peritoneum and parapancreatic tissue, fixing the pancreatic stump, are performed along the margin of the mesentery of the intestine and tied; 4 — the closing row of sutures of the mesentery and intestinal wall; 5 — serous-muscular sutures of the posterior wall of the jejunum are held and tied; 6 — serous-muscular sutures of the anterior wall of the jejunum.

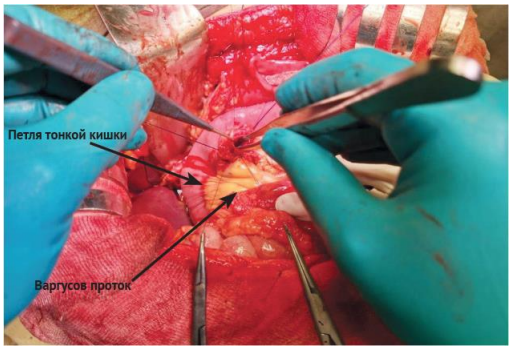


Fig. 6. Formation of end-to-loop pancreatoenteroanastomosis.

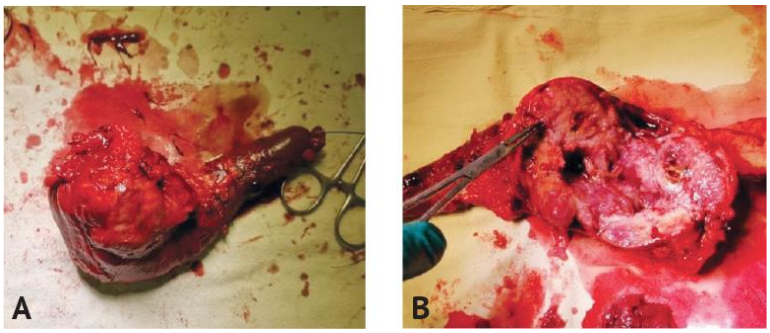


Fig. 7. Removed pancreatoduodenal complex (A), sectional tumor (B).

Histological examination of the operating material revealed signs of a neuroendocrine tumor of the head and body of the pancreas with invasion into the muscular membrane of the duodenum, into the wall of the common bile duct - pT3NxM0IIA stage.

In the early postoperative period the patient was in the surgical intensive care unit, where intensive therapy was carried out, including antibacterial (ceftriaxone 2 g / day, quinisole 1 g / day for 5 days), antisecretory (octreotide 0.9 μg / day for 5 days), analgesic (ketoprofen 100 mg 2 times / day), infusion, anticoagulant (heparin 15 thousand units for 5 days), gastroprotective (omeprazole 40 mg / day for 5 days) therapy, correction of water-electrolyte disturbances.

On the 4th day of the postoperative period, non-occlusive thrombosis of one of the peroneal veins was detected without signs of flotation (grade I according to *Clavien – Dindo*). The dosage of heparin was increased to 20 thousand units. In a stable condition, on the 4th day of the postoperative period, the patient was transferred to the surgical department, where therapy was continued in full.

On the 4th day, there was a sharp deterioration in the patient's condition, the onset of aphasia, hemiparesis on the right. Glasgow coma scale - 12 points, stable hemodynamics, adequate breathing were noted. According to CT examination of the brain, ultrasound of the great vessels of the neck and transcranial Doppler ultrasonography (DPG), no pathological findings were found. Anticoagulant therapy was continued (Heparin 5000 U 4 times a day), antiplatelet therapy was started (Acetylsalicylic acid 100 mg 1 time a day). After 4 hours, an improvement was noted, consciousness was restored, and focal neurological symptoms regressed. So, transient ischemic attack was diagnosed.

On the 5th postoperative day the drainage tubes were removed from the abdominal cavity. On the 6th day the patient complained of numbness and muscle weakness in the left hand. DPG revealed occlusive thrombosis of the left axillary artery. Thrombextraction from the left brachial artery was performed (grade IIIa according to *Clavien-Dindo*).

Echocardiography revealed a defect in the interatrial septum, as well as pulmonary hypertension, in connection with which CT of the lungs and perfusion scintigraphy of the lungs were performed, bilateral massive PE with a perfusion deficit of 30–35% (grade I according to Clavien – Dindo) was revealed. A probable source of widespread thrombosis caused by non-closure of the foramen ovale was venous thrombosis of the lower extremities. Heparin therapy 30 thousand units in the form of extended infusion was prescribed. On the 7th day after the operation, the patient had a fever up to 38 ° C. A positive result of the polymerase chain reaction (PCR) smear for *COVID*-19, as well as infiltrative-inflammatory changes in the lungs of mild severity (CT-1), with an average probability of viral etiology on CT, were revealed. For further treatment, the patient was transferred to the infectious diseases department (Fig. 8).

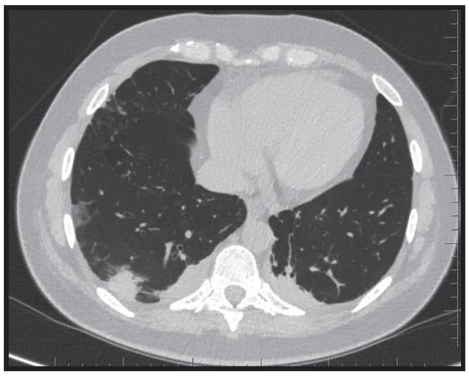


Fig. 8. Chest computed tomography dated Oct 17, 2020

Upon admission to the intensive care unit (ICU) of the infectious diseases department, the patient complained of weakness, headache and shortness of breath. Body temperature 38.1 ° C. Pulse 64 beats / min, BP 110/65 mm Hg, sinus heart rhythm. The respiratory rate is 15–19 per minute. SpO2 when breathing in atmospheric air 96%. The abdomen was somewhat swollen, soft on palpation, pain persisted, localized in the area of the postoperative wound. Urination without features.

Infusion, anticoagulant (Heparin 30,000 IU in the form of prolonged infusion), antiplatelet (Acetylsalicic acid 100 mg / day) and gastroprotective (Omeprazole 40 mg / day) therapy was continued.

Antibody levels to *SARS-CoV-2: IgM* 0.52*, IgG* 1.91. A dose of virus-inactivated fresh frozen plasma (FFP) of convalescents was transfused with a titer of 1: 320. The patient tolerated the transfusion satisfactorily. One day after transfusion, the titer of antibodies: *IgM* - 0.56, *IgG* - 17.31. The maximum body temperature per day is 36.9ºC. Patient's hemodynamics remained stable, breathing was adequate. The feeding was carried out per os, there was a stool, gases left. Control ultrasound of the veins of the lower extremities showed non-occlusive thrombosis of one of the peroneal veins on the right without signs of flotation.

On the 4th day of being in the ICU of the infectious department, CT scan of the chest organs was carried out, there was a positive trend in the form of a decrease in the zones of infiltration (Fig. 9).

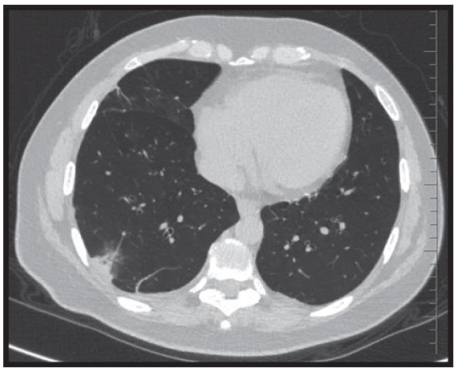


Fig. 9. Chest computed tomography dated Oct 20, 2020

After stabilization of her condition, she was transferred to the clinical department of the infectious diseases building. A transition was made to subcutaneous administration of heparin at a dose of 5000 U 4 times a day, then the patient was transferred to warfarin at a dose of 2.5 mg 2 times a day. The selection of the dose of warfarin was made under the control of the International Normalized Ratio (INR).

During the observation period in the clinical department (5-8 days of hospitalization in the infectious hospital), the patient's condition was moderate. Neurological symptoms were not detected, there were no dysfunctions of vital organs. The circulation in the left hand was compensated. The wound healed after the performed PDR, the stitches were removed. Under INR control, the adjusted daily dosage of warfarin was 2.5 mg.

На 8-е сутки нахождения в инфекционном корпусе (21-е с момента поступления в НИИ СП им. Н.В. Склифосовского) пациентка была выписана в удовлетворительном состоянии. ПЦР рибонуклеиновой кислоты *SARS-CoV*-2 был отрицательным, *IgM* 1,57, *IgG* 19,18 (рис. 10–13).

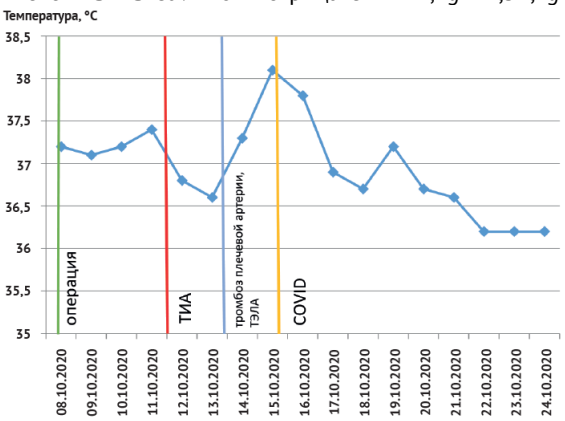


Fig. 10. Body temperature

Notes: TIA — transient ischemic attack; PE — pulmonary embolism

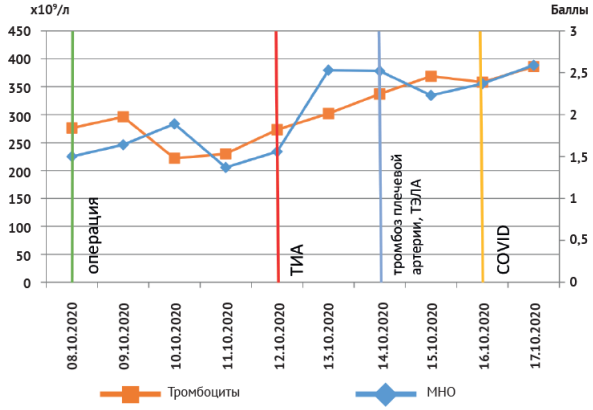
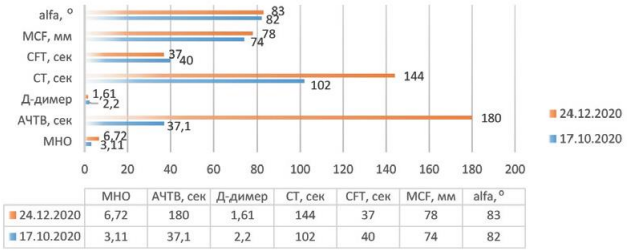


Fig. 11. The international normalized ratio and blood platelet levels

Notes: INR — international normalized ratio; TIA — transient ischemic attack; PE — pulmonary embolism



	МНО	АЧТВ, сек	Д-димер	CT, сек	CFT, сек	MCF, мм	alfa, °
24.12.2020	6,72	180	1,61	144	37	78	83
17.10.2020	3,11	37,1	2,2	102	40	74	82

Fig. 12. Rotational thromboelastometry

Notes: APTT — activated partial thromboplastin time; INR — international normalized ratio; MCF — maximum clot firmness; CT — clotting time; CFT — clot formation time

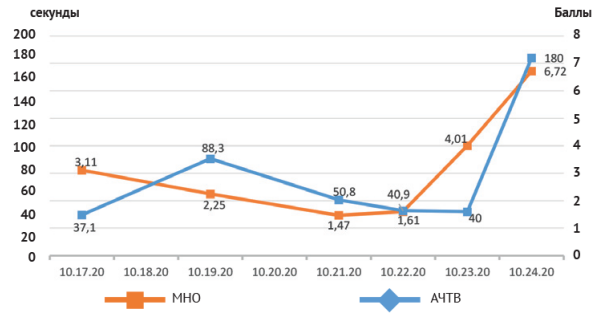


Fig. 13. Activated partial thromboplastin time (APTT) and international normalized ratio (INR) during the period of hospitalization in the infectious diseases department with a diagnosis of COVID-19

DISCUSSION

The given clinical observation illustrates a patient who developed a series of thromboembolic complications in the early stages after PDR performed for a neuroendocrine tumor of the pancreas head. Oncological disease, extensive surgery such as PDR, the postoperative period are risk factors for the development of various thromboembolic complications [9]. According to the literature, the incidence of thromboembolic complications after performing PDR ranges from 3–3.3% [10]. However, such a number of both venous and arterial thrombosis and thromboembolic complications in one patient really is casuistic observation. The open oval window cannot explain such a number of thromboembolic complications in one patient, since the frequency of occurrence and "occurrence" is actually also a frequency, therefore the phrase, the meaning of which is "frequency of frequency" looks awkward. Correct or not - at the discretion of the authors of this anatomical defect is 15–35% [11].

In the above observation, the debut of thrombotic complications probably coincided with the infection of the patient with *SARS-CoV-2*. The development of various thromboembolic complications is characteristic of *COVID*-19 [12]. The pathogenesis of *COVID*-19 lies in the imbalance of the renin-angiotensin system (RAS) and the immune system. The imbalance in the RAS is due to the peculiarities of the penetration of the virus into the host cells, for which the *S*-protein of the virus uses receptors for the angiotensin converting enzyme II (ACE II) [13]. One of the consequences of the developing RAS imbalance is pathological activation of platelets and vascular endothelium and, accordingly, thrombus formation. [14].

The key event in the pathogenesis of *COVID*-19 is the pathological activation of the immune system in response to the invasion of the *SARS-CoV-2* virus with the formation of the so-called cytokine storm [15]. A cytokine storm, as a rule, manifests itself with clear signs of immunothrombosis due to hyperactivation of platelets, damage to the vascular endothelium, vascular endothelium during a cytokine storm is not hyperactivated, the endothelium is damaged and, collapsing, releases into the bloodstream pro-inflammatory cytokines and other mediators of inflammation that support and enhance cytokine waves, fibrinogen, von Willebrand factor, coagulation factor [16]. Immune thrombosis in *COVID*-19 is so typical and characteristic that recently a special term has been formulated that reflects the essence of changes in the hemostasis system in *COVID*-19. It is *COVID*-19-associated thrombotic microangiopathy. [17]. The spectrum of states of thrombotic microangiopathy includes catastrophic antiphospholipid syndrome, hemolytic uremic syndrome, atypical hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation [18]. The distinctive features of any form of thrombotic microangiopathy are two: (1) the impossibility of preventing the development of thromboembolic complications using anticoagulant and antiplatelet therapy in prophylactic doses; (2) thrombosis of arterial and venous vessels of various diameters [19]. This is the situation that developed in the described clinical observation.

Fortunately, the course of COVID-19 in the above observation was not severe. Pathogenetic therapy in the form of FFP of convalescents with a high titer of antibodies and balanced anticoagulant and antiplatelet therapy led to recovery from coronavirus infection and normalization of disorders of the hemostasis system. Timeliness and adequacy of the therapy made it possible to avoid the development of organ disorders against the background of developed venous and arterial thrombosis.

CONCLUSIONS

The given clinical observation indicates that the reason for the atypical course of the postoperative period when performing PDR in patients with tumor damage to the pancreas may be conditions that are not directly related either to the pathology of the gland or to the peculiarities of the surgical intervention. When analyzing the patient's status, the conditions of the pandemic of the new coronavirus infection should be taken into account. Pathological, not explainable by other reasons, a hypercoagulable state may be a manifestation of *COVID-19*. Especially, this applies to clinical conditions with an asymptomatic or mild course of the disease, when there is no damage to the lung parenchyma, but the developing imbalance of the renin-angiotensin and immune systems leads to clinically significant disorders of the hemostasis system. In such situations, timely detection of *COVID-19* and adequate correction of therapy can fundamentally change the outcome of the disease.

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Received on 05.04.2021

Review completed on 12.05.2021

Accepted on 29.06.2021