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A case report of severe acute pancreatitis with infected necrosis and concomitant Coronavirus Disease-19 (COVID-19): a nosocomial infection or delayed respiratory manifestation of viral disease?

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The association between COVID-19 and acute pancreatitis (AP) has been extensively analyzed in recent research and review papers worldwide. It should be noted that most studies have focused on AP as a COVID-19 complication and/or an extra-pulmonary manifestation of the disease, although the investigation reports on the cases of prior pancreatitis and subsequent COVID-19 infection are limited.

The aim of this case report is to describe the treatment protocol and clinical outcome of a patient with acute necrotizing pancreatitis who developed nosocomial COVID-19..

Case presentation. The data were collected from patient S., a 42-year-old male admitted with AP to the intensive care unit of Kyiv City Clinical Emergency Hospital, in October 2020. This study was reviewed and approved by the local Ethics Committee (Protocol No 25-15-60). The patient signed written informed consent to participate in the study, after having been informed of all relevant aspects that could influence his decision.

The patient, primarily diagnosed with AP, was admitted to the hospital without a PCR test for detecting SARS-CoV-2. 21 days after his admission to the hospital, the patient developed COVID-19. AP progression to severe AP with infected necrosis, the development of systemic inflammatory response syndrome and multiple organ failure necessitated operative pancreatic debridement, which was postponed due to severe acute respiratory failure. Operative pancreatic debridement was performed on the 45th day of hospital stay after the resolution of COVID-19-associated *pneumonia*. The postoperative period was typical for the disease severity and the extent of the surgery, and was complicated by external pancreatic and colonic fistulas. The length of hospital stay for this patient was 115 days which included 20 days of treatment and monitoring in the intensive care unit due to *pneumonia*. He was discharged after clinical symptom improvement.

Conclusions. It is imperative to screen patients presenting with AP for SARS-CoV-2 in order to avoid misdiagnosis and inappropriate treatment strategy. Further detailed investigation of mechanisms of pancreatic injury in patients with SARS-CoV-2 is necessary.

Keywords
Acute necrotizing pancreatitis, SARS-CoV-2, COVID-19.

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The association between Coronavirus disease 2019 (COVID-19) and acute pancreatitis (AP) is comprehensively presented in numerous case reports, a few case cohort studies and review papers since the onset of the COVID-19 outbreak [4, 5, 7]. It's currently assumed that the causative agent of COVID-19 (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) has a wide range of cellular targets including those in the lungs, kidneys, liver, heart, brain, blood and etc. [19]. The multitarget nature of COVID-19 infection can be primarily explained by the expression of angiotensin-converting enzyme 2 (ACE2) in various organs, since it acts as the receptor to which the SARS-CoV-2 Spike glycoprotein (S) binds to invade the cells [11].

Consequently, COVID-19 can induce numerous extrapulmonary manifestations including gastrointestinal (GI) ones. GI manifestations of COVID-19 most commonly include but are not limited to dysgeusia, nausea, vomiting, diarrhea, and abdominal pain [15]. In the pancreas, SARS-CoV-2 receptive molecules are expressed by exocrine cells, β-cells, as well as pericytes [14]. Most of the studies focus on COVID-19-associated AP [5]. However, the information on the cases of nosocomial COVID-19 in AP patients is scarce [8]. Prognosis of AP course and evaluation of the disease severity in presence of nosocomial COVID-19 are quite complicated, and require the accumulation and analysis of clinical experience. This case report describes the treatment protocol and the clinical outcome of the patient with acute necrotizing pancreatitis and concomitant nosocomial COVID-19.

Case presentation

Herein we report the case of treatment of the patient with AP who developed nosocomial COVID-19. Written informed consent was obtained from the patient and the local Ethics Committee approved the publication of the case (Protocol No 25-15-60). A 42-year-old obese male patient S. with a body mass index (BMI) of 35 kg/m^2 and suspected AP was delivered to the Kyiv City Clinical Emergency Hospital by the medical team of the Center for Emergency Care and Disaster Medicine, Kyiv, on October 17, 2020. On admission, the patient, presenting with pain of 9-hour duration, reported long-term alcohol intake and fatty food consumption prior to seizures. The patient claimed that he didn't have any contact with a COVID-19-positive person as well as any symptoms of viral disease. For these reasons, diagnostics of COVID-19 was not conducted. Physical examination revealed abdominal bloating, sharp pain in the epigastric region, weakened peristalsis,

Table 1. **Laboratory findings throughout the course of the disease**

Parameter	Day 1	Day 66	Day 80	Day 87	Laboratory reference range
Hemoglobin, g/L	181	62	79	95	130—160
Hematocrit, %	54	20	26	31	40—48
RBC count, 10^6/μl	5.4	2.2	2.7	3.2	4.5—5.9
WBC count, 10^3/μl	18.2	6.4	11.3	9.7	3.9—10
PLT count, 10^3/μl	410	198	513	454	180—320
Aspartate aminotransferase (AST), μkat/L	0.48	0.19	0.41	0.56	0.1—0.45
Alanine aminotransferase (ALT), μkat/L	0.44	0.37	0.42	0.45	0.1—0.68
α-amylase (AML), U/L	365.0	39.9	41.0	23.4	12—32
Glucose, mmol/L	30.2	8.7	8.4	10.7	3.3—6.5
Creatinine, μmol/L	190	151	67	83	71—106
Blood urea nitrogen, mmol/L	8.2	2.0	7.3	10.0	2.5—8.3
Total serum protein, g/L	50	54	70	71	60—83
Total bilirubin, μmol/L	30.5	10.5	10.2	12.4	2—21
Direct bilirubin, 0—5 μmol/L	8.0	2.3	1.8	2.9	0—5

and dry tongue. The patient was hemodynamically stable and presented with a heart rate of 112 beats per minute, blood pressure of 158/90 mm Hg, and a temperature of 37.5 °C. Controlled hypertension was reported by the patient as the only comorbidity. The admission laboratory testing showed elevated blood amylase, pronounced leukocytosis, increased total and direct bilirubin (Table 1).

Elevated creatinine level (190 μmol/L) indicated moderate renal failure according to the revised Atlanta classification and Marshall scoring system [3]. Furthermore, the patient was diagnosed with new-onset diabetes mellitus considering an increase in blood glucose to 30.2 μmol/L. Ultrasound of the abdomen showed enlarged and edematous pancreas, as well as free fluid in the abdominal cavity. A chest X-ray on admission didn't not exclude moderate left lower lobe pneumonia and left-sided hydrothorax.

According to the local protocol, the patient was admitted to the intensive care unit, where his condition was managed using the «rule of four catheters» (a catheter for epidural anesthesia, the placement of an enteral feeding probe beyond the ligament of Treitz, the central vein catheterization, the programmed laparocentesis with evacuation of 250 ml of fluid) [18]. In the intensive care unit, the patient underwent fluid resuscitation with balanced isotonic crystalloid solutions (5.6 L/24 h), epidural analgesia (bupivocaine 3 ml every 3 hours) with blood pressure control and enteral tube feeding (25—35 % of the total fluid volume) as well as received pantoprazole 120 mg/24 h,, insulin 10 U/24h, antibiotic prophylaxis with leflocin (500 mg. i.v., twice daily), metrid (1 g, three times a day), and ceftriaxone (1 g i.v., twice daily) on the third day of hospital stay (October 19, 2020).

The patient was transferred to the surgical department on the 4th day from the onset of the disease (October 20, 2020). Ultrasound monitoring, which was carried out on day 7 (October 23, 2020), revealed fluid accumulation in the omental bursa up to 500 ml. Consequently, its puncture and drainage were performed using a catheter Pig tail 9 Fr. On day 17 (November 2, 2020), the fluid drainage was carried out and 600ml of fluid were removed from the left paracolic retroperitoneal space. On day 19 of the disease (November 5, 2020), spiral computed tomography (SCT) revealed destructive pancreatitis with infiltration of parapancreatic tissue spreading to the omental bursa, spleen gate, duodenum and stomach as well as the root of the small-bowel mesentery.

On day 20 (November 6, 2020), the patient's condition deteriorated due to progressive respiratory failure (SpO2 86 %). The patient tested positive for

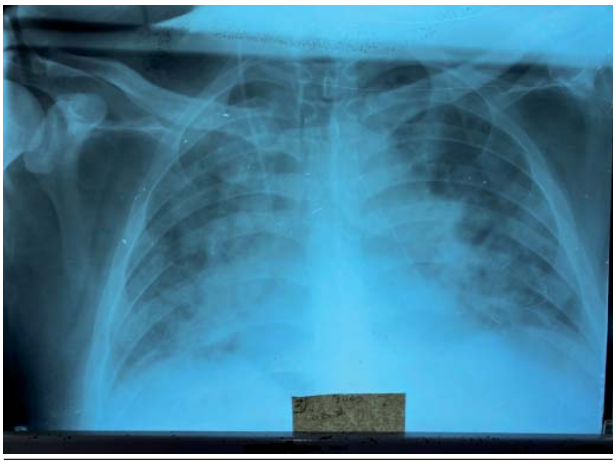

Figure 1. **Chest X-ray image of the patient S. with AP after the PCR-confirmed COVID-19 infection on the 20th day of hospital stay**

COVID-19. A chest X-ray revealed bilateral polysegmental pneumonia (Fig. 1). On day 21 (November 7, 2020), progressive respiratory failure was observed (SpO2 82 %), and endotracheal intubation with mechanical ventilation was performed. On day 24 (November 10, 2020), the patient underwent extubation followed by humidified oxygen insufflation through a face mask and nasal catheters. On day 27 (November 13, 2020), the patient was transferred to the surgical department as well as insufflated with humidified oxygen (4—10 L/min) due to his oxygen-dependence.

The objective examination (purulent discharge through drainage) and signs of SIRS (temperature > 38 °C; heart rate > 90 beats/min; WBC

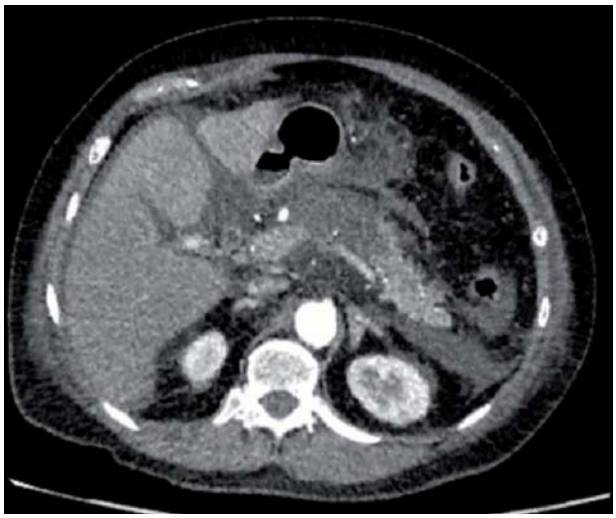

Figure 2. **Abdominal SCT scan showing destructive pancreatitis with parapancreatic infiltrate, formation of limited peritoneal fluid accumulations, mesenteric and peritoneal lymphadenopathy, and bilateral hydrothorax**

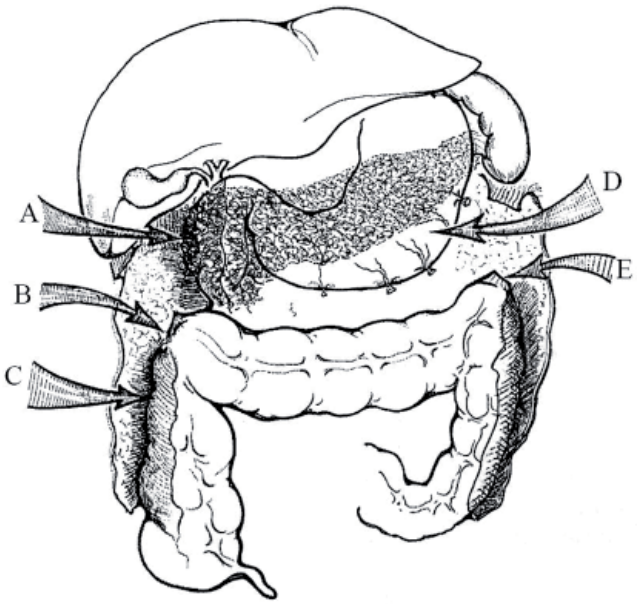

Figure 3. **Schematic representation of the operative decompression of the retroperitoneal spaces:** A — hepatic flexure of colon; B — right paracolic retroperitoneal space; C — the tail area of the pancreas; D — splenic flexure of the colon; E — left paracolic retroperitoneal space

count > $12 \cdot 10^9$/L) necessitated surgery, but it was postponed due to signs of respiratory failure.

SCT performed on day 40 (November 26, 2020) revealed destructive pancreatitis with parapancreatic infiltration, formation of limited peritoneal fluid accumulations, mesenteric and peritoneal lymphadenopathy, and bilateral hydrothorax (Fig. 2).

On day 45 of the disease (December 1, 2020), open operative pancreatic debridement (OPD) was performed. Several areas of necrotic lesions were identified, including paraduodenal and right lateral canal area, parapancreatic area, root of the small-bowel mesentery and left paracolic retroperitoneal space. In this case, the Kocher mobilization of the duodenum and hepatic flexure of colon were performed along with the dissection of splenic-colon and colon-diaphragmatic ligaments, parietal peritoneum of the left lateral canal outward from the descending part of the colon and mobilization of splenic flexure (Fig. 3).

The postoperative period was typical for the disease severity and the extent of the surgery, and was complicated by external pancreatic and colonic fistulas.

Serum level of α-amylase and WBC count were progressively decreasing during post-surgery period, and reached normal value on day 87 (see Table 1). Glucose level was also decreasing, but exceeded the reference range. Along with mild elevation of AST level and moderately increased serum creatinine, it indicated ongoing diabetes. The patient was discharged after clinical symptom improvement.

Discussion

Increasing number of cases of coexistence of AP and COVID-19 necessitate studying clinical experience on this issue. In most cases, AP is regarded as the secondary or even primary presentation of COVID-19 considering the tropism of SARS-CoV-2 to different tissues including pancreatic and parapancreatic ones [11, 19]. It presumably causes GI symptoms of COVID-19, which mimic typical AP manifestations. In all these cases, patients have ongoing COVID-19 infection, confirmed by the results of PCR-test and CXR/CT, at the time of AP onset. The most common features of AP are the absence of similar attacks in the past medical history, most often the absence of any other etiological factors that could cause the development of the disease (excessive alcohol and fatty food consumption, trauma, gallstone migration and etc.) as well as mild course of the disease (results of CT) with moderate abdominal pain [2, 10, 12, 16]. In addition, AP can develop as the complication of the underlying COVID-19. At the time of AP onset, PCR-test can be negative and patients can be presented with resolved pneumonia, therefore, AP can be an early presentation of COVID-19-associated multisystem inflammatory syndrome [1, 17].

In our case, a different picture of the AP and COVID-19 association was observed when typical symptoms of coronavirus infection were secondary to AP and developed in presence of pancreatitis symptoms. Similarity of the clinical pattern of these diseases significantly complicates diagnosis in the absence of molecular detection of the pathogen. GI symptoms are widely reported for patients with COVID-19. SIRS signs are typical for both pathologies. Moderate respiratory failure in AP patients could mimic mild COVID-19 course. Even new-onset diabetes mellitus, which is noted as the commonest comorbidity in COVID-19 [13], is also inherent to AP [20].

Our assumption concerning the nosocomial origin of COVID-19 was based on the course of the inflammatory component of AP. It is well documented that SIRS lasts about 14 days in patients with AP, gradually leading to compensatory systemic anti-inflammatory syndrome (CARS) with compromising immune system patrolling function and increased risk of infection [6]. Nevertheless, the presence of COVID-19 cannot be excluded

on admission, since according to Galanopoulos et al., 2020, patients, presenting exclusively with GI symptoms, have delayed diagnosis of COVID-19 and in their case the first respiratory symptoms appear later [9]. Therefore, it can be assumed that viral infection of the pancreas along with excessive alcohol and fatty food consumption reported by the patient on admission triggered pancreatitis. COVID-19 diagnostics on admission could facilitate decision making and prediction of the clinical course of the disease.

Conclusions

Although there is no satisfactory evidence showing that COVID-19 can cause AP or negatively influence prognosis, we consider that it is mandatory to screen patients presenting with AP for SARS-CoV-2 in order to avoid misdiagnosis and inappropriate treatment strategy. A deep insight into the mechanisms of SARS-CoV-2 pancreatic injury is needed for exploiting a causal relation between these two entities in differential diagnostics.

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Declaration of interests

The authors declare that they have no conflicts of interest.

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Ethics approval and written informed consents statements

The project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects of Kyiv City Clinical Emergency Hospital (Kyiv, Ukraine), based on the Declaration of Helsinki. Patient gave his written informed consent prior to study inclusion.

Author contributions

Y. Susak: chief surgeon, performed the OPD on patient who was included in this study; O. Lobanova: data interpretation; O. Tkachenko: supervisor, design of the study; L. Skivka: drafting the manuscript, data analysis.

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Повідомлення про випадок тяжкого гострого панкреатиту з інфікованим некрозом та супутньою коронавірусною хворобою-19 (COVID-19): внутрішньолікарняна інфекція чи відтермінований респіраторний вияв вірусної хвороби?

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Взаємозв'язок між коронавірусною хворобою-19 (COVID-19) та гострим панкреатитом (ГП) широко обговорюється у дослідницьких та оглядових публікаціях. У більшості праць ГП розглядають як ускладнення COVID-19 та/або позалегеневий вияв захворювання. Значно менше уваги приділяється випадкам панкреатиту з наступним розвитком COVID-19.

Метою цього звіту є опис протоколу та клінічних результатів лікування пацієнта з гострим некротичним панкреатитом, у якого розвинулася внутрішньолікарняна COVID-19.

Клінічний випадок. Пацієнт С. (чоловік, 42 роки) госпіталізований з попереднім діагнозом ГП у відділення інтенсивної терапії Київської міської клінічної лікарні швидкої допомоги у жовтні 2020 р. Протокол дослідження було розглянуто та схвалено місцевим комітетом з біоетики (протокол № 25-15-60). Письмова інформована згода отримана від пацієнта після пояснення змісту дослідження.

У пацієнта з первинним діагнозом ГП, якому на момент госпіталізації не проводили виявлення за допомогою полімеразної ланцюгової реакції коронавірусу тяжкого гострого респіраторного синдрому-2 (Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)), через 21 день після надходження до лікарні було діагностовано COVID-19. Прогресування ГП (до тяжкої форми з інфікованим некрозом, синдромом системної запальної реакції та поліорганною недостатністю) потребувало панкреатонекрсеквестректомії, яку було відкладено через тяжку гостру дихальну недостатність. Операцію проведено на 45-ту добу перебування у лікарні після усунення пневмонії, пов'язаної з COVID-19. Післяопераційний період перебігав відповідно до тяжкості захворювання та об'єму операції і був ускладнений зовнішніми панкреатичною та товстокишковою норицями. Пацієнт перебував у лікарні впродовж 115 діб, з них 20 діб був під наглядом у відділенні інтенсивної терапії, призначеному для випадків пневмонії. Він був виписаний після поліпшення симптомів у задовільному стані.

Висновки. На момент госпіталізації пацієнтів з попереднім діагнозом ГП слід проводити скринінг на наявність SARS-CoV-2 з метою уникнення помилкового діагнозу та оптимізації стратегії лікування, з огляду на подібність симптомокомплексу ГП і абдомінальних симптомів позалегеневої маніфестації COVID-19. Глибокого вивчення у контексті існуючої коморбідності потребують механізми ураження підшлункової залози SARS-CoV-2.

Ключові слова: гострий некротичний панкреатит, SARS-CoV-2, COVID-19.

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