CASE REPORT

Case Report of Fatal Acute Necrotizing Pancreatitis in Patient with COVID-19: We Should Be Aware Of Hemorrhagic Complications

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ABSTRACT

Objective COVID-19 primarily affects the respiratory tract, but reports of acute pancreatitis occurrence in patients with COVID 19 suggest possibility of direct injury of pancreatic gland by this virus. **Methods** We present observation of patient with acute necrotizing pancreatitis and concomitant COVID-19. SARSCoV2 infection was diagnosed 5 days before initiation of ANP with bilateral pneumonia. He was admitted with persistent multi-organ failures and injuries over 50% of pancreas. **Results** Biochemical changes included prolonged prothrombin and partial thromboplastin time, elevated fibrinogen and D-dimer concentration, hypertriglyceridemia with normal amount of platelets. Diffuse erosive hemorrhage from pancreas occurred on 6th day from onset as result of coagulopathy and several laparotomic interventions were necessary for control of it. Despite intensive therapy this patient died due to progressed ARDS. **Conclusion** Development of ANP in patients COVID-19 carries risk of erosive hemorrhage from pancreas due to coagulopathy. Precise monitoring of coagulation and fibrinolytic activity in such patients is indicated.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARSCoV2) has led to an unprecedented global health crisis. To date, over 19 million of cases of coronavirus disease 2019 (COVID-19) are confirmed [1]. The severity of the disease ranges from subclinical infections to severe illness requiring critical care measures [2, 3] and fatality rate is reported to reach as high as 15% in some countries. COVID-19 infections primarily affect the respiratory tract [4], but gastrointestinal symptoms such as nausea, vomiting and diarrhea also occur [5] and an abdominal pain is most frequent in patients who are severely ill. Presence of viral RNA in fecal specimens was found despite negative respiratory tests [6] indicating important role of gastrointestinal tract in COVID-19 pathogenesis. It was established that viruses such as mumps, Coxsackie B, measles, Epstein–Barr and hepatitis A, B and E can cause acute pancreatitis (AP) [7]. Taking in account previous reports of AP development in patients with COVID 19 suggests possibility of direct injury of pancreatic gland by SARSCoV2.

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Keywords COVID-19; Pancreatitis, Acute Necrotizing
Abbreviations ANP acute necrotizing pancreatitis; ARDS acute respiratory distress syndrome; COVID–19 coronavirus disease 2019
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CASE REPORT

We present a case of fulminant acute necrotizing pancreatitis in a patient with concomitant COVID-19. Informed consent was obtained from the patient's family and the local ethic committee approved the publication of case. He was 39 years old with BMI 34.7 kg/m^2 with no history of diabetes mellitus. He had gallbladder stones without previously documented attacks of acute cholecystitis. He was diagnosed with COVID-19 on July, 15, 2020 by analyzing nasopharyngeal swab samples with real-time polymerase chain reaction (RT-PCR; Roche, Switzerland), secondary test confirmed diagnose. There were no changes on lung X-ray but thoracic CT showed bilateral pneumonia with an injury of about 15% of lungs **(Figure 1)**. He was treated at home with umifenovir and azithromycin. On the 5th day after the onset of COVID-19 infection he got an acute severe pain with nausea and multiple cases of vomiting after bowing down. He tried to continue self-treatment without improvement. Next day he was admitted to the local hospital and he was diagnosed biliary acute pancreatitis (AP). The intensive therapy included infusion of 3.5 l of balanced electrolytic solutions, injection of painkillers, a spasmolytic agent, octeotride and meropenem. Despite treatment, the patient's condition did not improve and he was transferred to our tertiary regional hospital. He was admitted to the critical care unit with severe AP, persistent renal failure, distended abdomen, signs of anxiety, hematocrit level of 50% and overall APACHE II score of 12 points. Hyperamylasemia, hypertriglyceridemia, mild hyperbilirubinemia, an

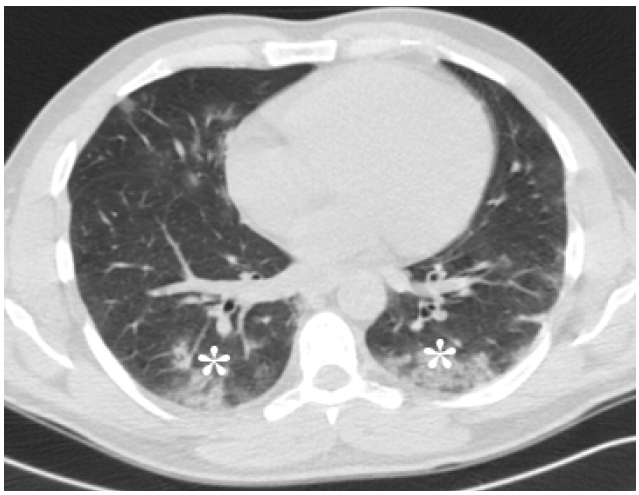

Figure 1. Chest CT on 4th day after diagnosis of COVID-19 infection.
* - Ground glass opacities

increased level of creatinine, urea and D-dimer, slightly prolonged prothrombin and partial thromboplastin time as well as elevated fibrinogen concentration with normal amount of platelets were found **(Table 1)**. Diffuse enlargement of all parts of pancreas with nonhomogeneous structure and low density non-bordered parapancreatic collections, right-side pleuritis were found in CT **(Figure 2)**. The multidisciplinary team decided to continue previously initiated treatment with some correction. The thoracic epidural catheter was introduced to improve analgesia and to stimulate intestinal peristalsis. Besides, metoclopramide, neostigmine and enemas were administrated, the right side thoracentesis was performed and an intra-abdominal drain was set to remove fluid from the abdominal cavity and to reduce intra-abdominal pressure (IAP). Taking in account high risk of thromboembolic complications of COVID-19 enaxoparine 40 mg s/c q12 hr was started and the administration of insulin 0.1 U/kg/h was initiated for reducing the level of hypertriglyceridemia. Fractional enteral feeding was initiated through nasojejunal tube. Despite intensive therapy the patient's condition continued to worsen – renal failure persisted, intestinal paresis and elevated IAP remained, his consciousness became depressed, an acute respiratory distress syndrome (ARDS) developed and SaO_2 decreased to 85% even with breathing by moist oxygen. Tracheal intubation was performed and artificial ventilation was started. On the 6th day after initiation of AP the IAP increased over 30 mm Hg and blood clots in tube from abdominal cavity were noticed. Acute erosive hemorrhage was suspected. Taking in account presence of intra-abdominal compartment syndrome we performed urgent laparotomy. There were 2 l of brown color fluid with fresh clots in the abdominal cavity. After opening the gastrocolic ligament the total pancreatic necrosis was established with the diffuse hemorrhage from a necrotic tissue and several spots of active bleeding that were sutured. An anterior surface of pancreas was covered with SURGICEL® Absorbable Hemostat and two 24 Fr silicone drainages were introduced to the omental bursa. Cholecystostomy was performed and the abdominal wall was closed by a zip. The Enoxaparin administration was canceled and the transfusion of fresh frozen plasma and an erythrocyte concentrate were started. The early postoperative period was followed with a cardiovascular failure; the system hemodynamics was corrected by the norepinephrine infusion. A renal daily output was maintained at the level of 900-1000 ml by a diuretics infusion. Enterococci feacalis was cultivated from necrotic pancreatic tissues and Zyvox 600 mg IV q12hr was added. Moderate stabilization was reached on the 4th day after initial surgery and planned relapatomy was performed. There was 1.5 l of brown color fluid in the abdominal cavity with a small amount of clots; some spots of bleeding below were still present. Additional SURGICEL® Absorbable Hemostat was applied and the abdominal cavity was closed by zip. Two days after the abdominal cavity was opened again, tampons were removed; no signs of bleeding were present. Partial necrosectomy was performed **(Figure 3)**, the omental bursa was closed according to Berger with additional access through a large diameter covered nitinol stent introduced through the laparotomic wound that was sutured **(Figure 4)**. Enterobacteria spp were cultivated from necrotic collections and the antibacterial therapy was changed to piperacillin/tazobactam. During the postoperative period repeated mini invasive necrosectomies were performed through a nitinol stent. Despite a correction of the antibacterial scheme and active intensive therapy the patient's condition did not improve and he died two days after as a result of the progressed respiratory failure. At autopsy, a severe distress lung injury **(Figure 5)**, renal dystrophy, almost total necrosis of pancreas but no purulent parapancreatic collections were estimated.

DISCUSSION

COVID-19 typically appears with pulmonary symptoms but its extra-pulmonary presentation has drawn significant attention. A recent study suggests that gastrointestinal symptoms can be as high as 50% and are presented by nausea (17.3%), diarrhea (12.9%), anorexia (12.2%), an abdominal pain (5.8%), belching (5%) and emesis (5%) [5, 6, 8]. Wang *et al*. were the first to describe 9 persons

Table 1. Changes of patient's laboratory data.

	ICU admission	1st surgical intervention	3rd surgical intervention
WBC,10^9/L	14,9	16,6	13,4
N to WBC ratio, %	82	86	89
L to WBC ratio, %	10	8	6
Ht, %	50	25	31
Hb, g/dl	144	76	94
PLTS,10^9/L	180	90	85
CRP, mg/L	215	225	258
PT, sec	15	17	13
aPTT, sec	41	50	30
D-dimer, µg/l	1.5	2.9	4.2
Fibrinogen, g/l	5.6	1.6	4.1
AST, U/L	51	46	42
ALT, U/L	61	58	50
Protein, mg/dl	64	59	52
Bilirubin, µmol/l	45	40	16
Glucose, mmol/l	11.2	10.6	10.4
Creatinine, µmol/l	164	636	468
Urea, µmol/l	10.5	18.5	14.6
Amilase, U/L	1200	140	60
Triglyceride, mmol/l	9.5	3.2	1.2
SaO_2, %	90	85	78
APACHE II score	12	19	26

ALT – alanine aminotransferase; aPTT – activated partial thromboplastin time; AST – aspartate aminotransferase; CRP – C-reactive protein; Hb – hemoglobin; Ht – hematocrit; L – lymphocytes; N – neutrophils; PLTS – platelets; PT – prothrombin time; WBC – white blood cells

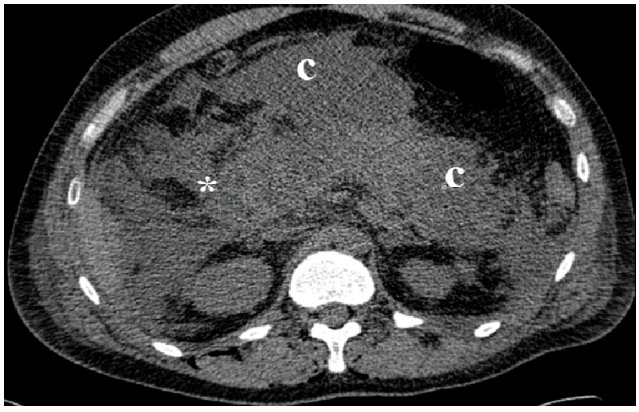

Figure 2. Abdominal CT on 5th day after onset of acute pancreatitis.
c- Acute necrotic collections
*- Common bile duct without signs of obstruction

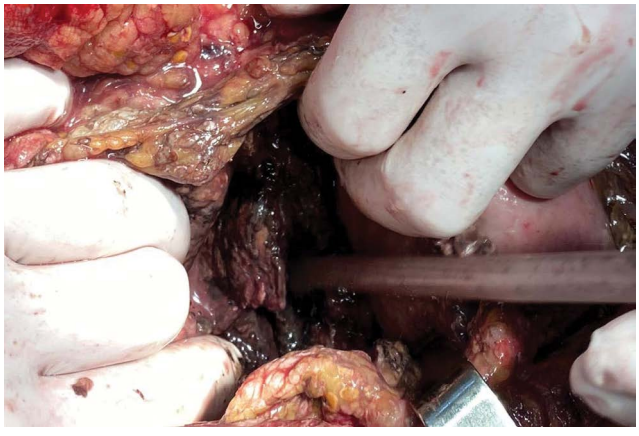

Figure 3. Necrosectomy through gastro-colic ligament.

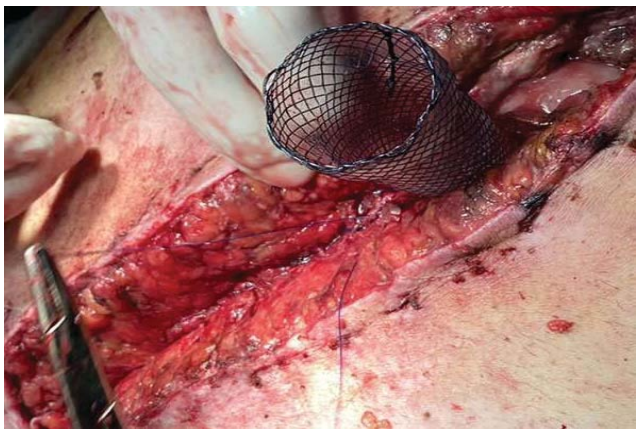

Figure 4. Drainage of omental bursa with nitinol stent.

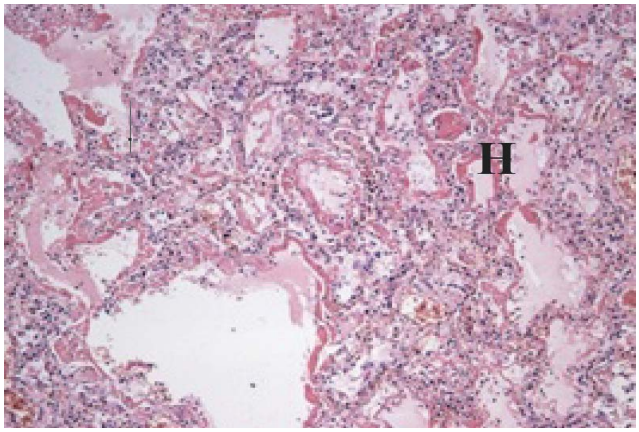

Figure 5. Microscopy of patient's lungs at autopsy.
H –Hialine membranes

with AP in a case series of 52 patients with COVID-19 [9]. Liu *et al*. also showed 17% incidence of the pancreatic injury in 67 severe COVID-19 cases although the injury was evident on CT scan in only 7.46% cases [10]. The incidence of pancreatic injury was low (1.85%) in patients with mild disease. Hadi *et al*. reported familial clustering of COVID-19 cases with two of three family members with COVID-19 who had AP [11]. Anand *et al*. reported a case of COVID-19 who initially presented with fever, cough, a sore throat and myalgia [12]. The AP was diagnosed on CT scan that showed diffusely edematous pancreatitis. None of the cases reported so far had necrotizing AP even though some were classified as severe, and none required any intervention for pancreatitis-related local complications. Although the clear pathogenesis is unknown, the AP in COVID19 could occur due to the direct cytopathic effect of local SARS-CoV-2 replication [10]. Another putative mechanism involves a dysregulated immune response induced by SARS-CoV-2 that targets pancreas in addition to the lungs and kidneys causing the AP besides organ failure [13].

Here we present a case of the fulminant necrotizing AP in a generally healthy overweight middle age patient who has got COVID-19 infection. He was diagnosed with gallbladder stones but without any previous attack of biliary colic or cholecystitis. His APACHE II score was 6 points at his primary admission to local hospital but progressed to 12 points 24 hours later when he was delivered to our center. His condition worsened next day despite the intensive therapy. We administered insulin and low molecular heparin (enoxaparin) to decrease serum triglyceride levels and to suppress a systemic inflammatory response. They stimulate lipoprotein lipase activity and accelerate chylomicron degradation [14]. Our decision to apply enoxaparin was dictated also by a high possibility of thromboembolic complications. Previously, coagulation and cardiac biomarkers have been described to be elevated in COVID-19 patients – they reflect an inflammatory status characterized by coagulation activation and are predictors of death [15]. It was shown that, despite the use of anticoagulant prophylaxis, the rate of venous and arterial thromboembolic complications in hospitalized COVID-19 patients was remarkable, approximately 8% [16]. It has been postulated that the administration of low molecular weight heparin during the earlier phases of the SARS-CoV2 infection may exert a positive effect not only through thrombosis prevention, but also reducing systemic and pulmonary inflammation, and limiting viral invasion [17, 18]. Lowering of triglyceride level 24 hours later was noticed but ARDS developed and a necessity for pulmonary artificial ventilation occurred. System oxygenation improved only moderately after initiation of ventilatory therapy: SaO_2 increased to 84-86% during the 1st and the 2nd day and to 90% – on the 3rd. Hemorrhagic pancreatitis was developed on the 4th day and a cardio-vascular failure aggravated the patient's condition during

the early postoperative period. Supportive measures permitted to perform two additional abdominal surgeries but the respiratory failure progressed.

CONCLUSIONS

Our observation of fulminant ANP in a patient with COVID-19 permits to speculate that $SARSCoV_2$ carries essential risk of hemorrhagic complications due to coagulopathy. Precise monitoring of coagulation and the fibrinolytic activity is indicated for such patients.

Conflict of Interest

The authors report no conflict of interest.

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