Review Article

The pancreas and COVID-19: a clinical conundrum

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Abstract: With the progression of the COVID-19 pandemic, the classic manifestations of COVID-19 (e.g., persistent fever, dry cough, pneumonia, and acute respiratory distress syndrome in the severe disease) have expanded to include less common complications of the extrapulmonary organs. Recent evidence has shown that COVID-19 patients with concomitant presence of GI symptoms are at higher risk of developing severe disease and have poor clinical outcomes. Recently, multiple SARS-CoV-2-induced acute pancreatitis (AP) cases have been reported. This literature review aims to provide an insight into SARS-CoV-2-directed invasion of the pancreas. We will also review the currently available literature on the clinical effects of SARS-CoV-2, including AP and mild elevation of lipase levels in patients with COVID-19. In addition, we will discuss plausible mechanisms that underly SARS-CoV-2-induced pancreatitis.

Keywords: COVID-19, pancreas, cytokines, SARS-CoV-2, lipase, amylase, pancreatitis

Introduction

In the past year, medical and scientific communities have provided an abundance of valuable insight into the epidemiology, pathogenesis, and clinical spectrum of coronavirus disease 2019 (COVID-19). COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. SARS-CoV-2 primarily affects the pulmonary system by the cytopathic effects elicited through viral replication and by overwhelming the immune system by cytokine storm [2]. As a result, the classical manifestations of COVID-19 include persistent fever, dry cough, pneumonia, and acute respiratory distress syndrome [1-3]. Nevertheless, SARS-CoV-2 also affects extrapulmonary organs. The viral particles and their receptors are also present in various human cells, including organs of the gastrointestinal (GI) tract, pancreas, cholangiocytes, brain, kidney, placenta, and other organ systems [4]. Extrapulmonary symptoms of COVID-19 are increasingly being identified and reported in the literature. Recent evidence has shown that COVID-19 patients with the simultaneous presence of GI symptoms such as nausea, vomiting, and diarrhea are at higher risk of developing severe disease and have poor clinical outcomes [5].

Recently, multiple SARS-CoV-2-induced acute pancreatitis (AP) cases have been published in the literature [6-8]. Most of these patients had no obvious cause of AP, and the occurrence of AP mostly coincided with a COVID-19 diagnosis [9, 10]. The causal relationship between the two is plausible because various viruses are one of AP’s known etiologies [11]. In particular, viruses such as hepatotropic virus (Hepatitis B virus being the most common), Coxsackie virus, cytomegalovirus (CMV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), mumps, varicella-zoster virus, and others have been shown to cause pancreatic inflammation [11]. The mechanism of action differs between these viral agents, varying from direct viral inju-
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Figure 1. The mechanistic rationale of SARS-CoV-2 elicited acute pancreatitis. A. Differential expression patterns of SARS-CoV-2 receptors in pancreatic cells can allow viral entry and thereby initiate acute pancreatitis or exacerbate an existing one; B. SARS-CoV-2 elicited lipotoxicity can initiate a pro-inflammatory cytokine storm to further aggravate acute pancreatitis, triggering acute respiratory distress syndrome and multiorgan failure.
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SARS-CoV-2 elicits lipotoxicity/cytokine storm and multiorgan failure

Although SARS-CoV-2 effects on the pancreas remain an active area of investigation, current models propose a link between the release of pancreatic lipase and elevations in unsaturated fatty acids [27, 28]. It was hypothesized that intestinal release of pancreatic lipase increased lipolysis and plasma levels of unsaturated fatty acids which could damage mitochondria and cause an increase in pro-inflammatory immune mediators (e.g., IL-6, IL-8, and IL-10). This increase in cytokines can accelerate the disease pathogenesis and lead to life-threatening multiorgan failure and acute respiratory distress syndrome (ARDS) (Figure 2) [16, 27, 28]. This fits with previous clinical studies which showed a link between cytokine storms in COVID-19 patients and increased morbidity and mortality rates in hospitalized patients. However, additional clinical studies and analysis are needed to further elucidate and confirm this hypothesis.

Acute pancreatitis (AP) in COVID-19 patients and their prognosis

The occurrence of AP in COVID-19 was reported by many case reports and retrospective studies. AP was diagnosed by following the revised Atlanta classification, which required that the patient needed to exhibit at least two out of three criteria, such as: (i) abdominal pain, (ii) serum amylase or lipase activity at least three times greater than the normal, and (iii) characteristic imaging of pancreatitis [29]. The patients were also diagnosed with COVID-19 by performing PCR on the nasopharyngeal swab [1]. The studies conducted in China, India, and United States reported a low incidence of AP in hospitalized COVID-19 patients [30-32]. Among hospitalized COVID-19 patients, AP was associated with higher morbidity and mortality rates [30]. In contrast, within the cohort of 42 participants, the mortality rate was 42.8% with no significant correlation to the amylase and lipase levels [31]. However, this study reported that 33% of patients exhibited hyperamylasemia, and 24.1% suffered from hyperlipidemias. This investigation, however, had its limitations, because the lipase levels were unavailable for all patients,
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and the imaging was not performed due to COVID-19-related restrictions at the time. Therefore, the proper AP diagnosis could be missing for all participants.

Furthermore, the manifestation and the outcome of the AP were exacerbated when the patient was diagnosed with COVID-19 [33, 34]. In comparison to the SARS-CoV-2 negative patients, the infection elicited increased multi-organ and persistent organ failure, which resulted in higher morbidity and mortality rates [33]. Furthermore, when pancreatitis was accompanied by COVID-19, patients had a longer hospitalization stay and required more help from the mechanical ventilator [34]. The outcome did not depend on the etiology of pancreatitis, and the patients with high alcohol consumption, gallstones, drugs, or hypertriglyceridemia, were taken into account while conducting these investigations [33, 34].

Multiple independent case reports have also described the progression of COVID-19 highlighted by the persistent abdominal pain, increased amylase, and lipase levels and imaging changes of pancreas indicative of AP [35-44]. The usual presentation included sharp abdominal pain, nausea, vomiting, and diarrhea around the time of the positive SARS-CoV-2 PCR test and the onset of disease symptoms [35-44]. The biochemical analyses revealed the elevated pancreatic enzyme levels, while the imaging scans showed either normal or atrophic pancreas with tail parenchymal enlargement and surrounding retroperitoneal fat stranding [35, 37-44]. Patients were held with nothing per os, intravenous fluids, and analgesics [35-44]. This was followed by the rapid decrease of the amylase and lipase levels. Patients were discharged after the abdominal and pulmonary symptoms were resolved without sequelae [35-44]. The manifestation of COVID-19-associated pancreatitis was unlike the usual disease [44]. Although the disease initially appeared severe, they reported a pancreaticoduodenal inflammation with steatosis [44]. Due to the idiopathic nature of AP in these patients, case reports argued for a differential diagnosis of the COVID-19 [35-37, 39-44]. The pancreatitis origin in the observed patient perhaps lay in the COVID-19 medication treatment, as the disease developed after the pulmonary issues were resolved upon therapy with acetaminophen, dexamethasone, ciprofloxacin, pantoprazole, and tocilizumab [38]. However, one case study reported that the AP developed in a patient with only

![Figure 2. Mechanisms of SARS-CoV-2-elicited pro-inflammatory cytokines (Interleukin-6, Interleukin-8, and Interleukin-10) that can mediate the development of acute pancreatitis.](Image)
mild respiratory tract symptoms and without any COVID-19 treatments [42].

A handful of case reports documented an AP diagnosis before the manifestation of the upper respiratory problems and the COVID-19 testing. These patients presented to the hospital with persistent GI-related complications, such as abdominal pain, diarrhea, and vomiting [8, 45-48]. Upon determining the lipase/amylase levels and performing the appropriate imaging, they were admitted with an idiopathic AP diagnosis [8, 45-48]. The patient’s sex, age, and prior underlying medical history were ruled out as contributing factors to the diagnosis. Upon hospitalization, many patients started developing respiratory issues and tested positive for the SARS-CoV-2 with the nasopharyngeal swab PCR [8, 45-48]. After this point, the manifestations of both AP and COVID-19 were congruent with each other. The resolution of one concurred with the other, followed by patient discharge without any visible permanent consequences. As pancreatitis manifested prior to the prominent systemic inflammation incited by the SARS-CoV-2 infection, these reports ignite the debate on the ability of the virus to directly affect the pancreas and elicit pancreatitis [8, 45-48]. Furthermore, recognizing that idiopathic AP can be one of the early manifestations of COVID-19 is important for physicians so that they can take additional precautions to protect themselves and minimize the spread.

Can lipase be a marker for pancreatic injury secondary to COVID-19?

A common laboratory marker for pancreatic injury is an elevation in lipase levels. The lipase is produced by the pancreatic acinar cells that enzymatically degrade fatty acids for uptake and subsequent metabolism [49]. When the pancreas is injured (e.g., pancreatitis), the increased permeability of acinar cells allows for the release of lipase into the blood. In general, lipase levels increase within three to six hours of injury, peak within 24 hours, and remain elevated for two weeks [49]. Although amylase is also used to detect pancreatic injury, lipase is preferred due to its higher specificity for pancreatic injury [49]. During the COVID-19 pandemic, several reports showed an elevation in lipase in COVID-19 patients with GI symptoms [35, 37-44]. Given this association, two retrospective studies examined the incidence and correlation of COVID-19 and pancreatitis to other factors, such as increased intensive care unit (ICU) admissions, intubation rate, leukocytosis, and abnormal liver enzymes [15, 50-53].

Of 83 COVID-19 patients in one study, 14 (17%) had elevated lipase levels greater than 3 times the upper limit of normal (ULN). Compared to patients with lipase levels less than 3 times the ULN, elevated lipase levels were associated with increased ICU admissions (92.9% vs. 32.8%), rate of intubation (78.6% vs. 23.5%), leukocytosis (22,000 white blood cells/μL vs. 10,400 white blood cells/μL), and abnormal liver enzymes (AST/ALT) (92.9% vs. 52.9%) [51]. Interestingly, there was a greater male predominance (78.6% vs.38.8%) in COVID-19 patients with elevated lipase levels compared to patients with lipase levels less than 3 times the ULN. A similar retrospective study examined 71 hospitalized COVID-19 patients with lipase enzyme laboratory information from 2 tertiary and 4 community hospitals in Massachusetts [50]. Among the 71 hospitalized COVID-19 patients, 12% had increased serum lipase levels [50]. In contrast, there was no difference in the rate of intubation, ICU hospitalization, gender, or mortality between COVID-19 patients with or without increased serum lipase levels [50, 51]. However, this study did not examine whether the patients had increased leukocytosis/white blood cells or liver enzymes in patients with increased serum lipase levels [51, 52]. Whether lipase levels correlates with the severity or mortality of AP related to COVID-19 remains an area of active investigation [52].

Pancreatic cancer and COVID-19

The COVID-19 pandemic also affected the chemotherapy regimens of pancreatic cancer patients, and placed them in a high-risk group for developing severe disease. Before the COVID-19 pandemic, only 20% of pancreatic cancers were eligible for surgery [54]. During the initial stages of the COVID-19 pandemic, triaging cancer patients for surgical resections was proposed based on the risk of treatment delay, disease progression, and patient’s age [55, 56]. In patients who were unable to proceed to surgery, chemotherapy was used during the interim period before surgical intervention. The long-term outcomes of cancer patients during the COVID-19 pandemic remain to be
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seen. Recent studies showed that the COVID-19 pandemic adversely impacted the delay of surgery for pancreatic cancer patients and the wait times for the diagnostic imaging. These delays often prevented patients from having their tumors resected [57, 58]. As a result, efforts to fast-track pancreatic cancer patients for assessment and treatment were set in place to improve the rates of successful pancreatic cancers resections [59].

Similar to other cancers, pancreatic adenocarcinoma patients have an increased expression of ACE-2 [60]. Further analysis showed that decreased methylation was correlated with increased ACE-2 expression in pancreatic adenocarcinoma [60]. However, ACE-2 expression in pancreatic adenocarcinoma did not affect a patient’s treatment, and it was not relevant to patients’ prognosis [60]. Furthermore, it remains uncertain whether continuing chemotherapy after contracting COVID-19 is safe. A recent case report described the outcome of the pancreatic cancer patient who was infected with COVID-19 seven days after starting his chemotherapy regimen [61]. After successfully recovering and showing a negative COVID-19 test result, he was re-started on his chemotherapy regimen without recurrence of COVID-19 [61]. However, SARS-CoV-2 positive patients undergoing surgical resection of pancreatic cancer require more appropriate supportive care [62].

Future directions

Whether AP is a direct result of COVID-19 remains an area of active investigation. Pre-existing conditions and increased inflammation from SARS-CoV-2 infection may increase the risk of pancreatic injury. However, the administration of monoclonal antibodies or other drugs, such as remdesivir, may also damage gastrointestinal organs leading to AP. There is little guidance on the therapeutic management of AP in COVID-19 patients. Although the revised Atlanta guidelines provides guidance for diagnosing AP, it may not be suitable for diagnosing AP in COVID-19 patients. The remaining uncertainties about several aspects of AP secondary to COVID-19 include the clinical course and the severity of disease, determining the early and late phase of the disease, and the inflammatory responses leading to shock and multisystem organ failure. It is also possible that increased levels of amylase and lipase may not correlate to the extent of pancreatic damage and do not really indicate AP. Without proper intervention, it remains unclear whether the pancreatic function remains permanently diminished or altered from the SARS-CoV-2 virus. Longitudinal studies are needed to assess the long-term effects of SARS-CoV-2 on the pancreas.

Despite several reports, it is unknown whether ethnicity may influence the frequency of AP in hospitalized COVID-19 patients. Minority groups, particularly Latino, American Indian, and African American populations, have higher hospitalization and mortality rates associated with COVID-19 than Caucasian patients [63]. It is believed that a combination of socioecono-mic factors and a higher prevalence of pre-existing medical conditions (e.g., diabetes, hypertension, obesity, asthma, and heart disease) increase the minority groups’ risk of contracting COVID-19. Therefore, minority groups may have a higher risk for developing AP from COVID-19 infections based on the increased COVID-19 infection rates in these communities. However, the biological factors that influence which COVID-19 patient will exhibit gastrointestinal and/or respiratory symptoms within each ethnic group remains unknown. Additionally, it is unknown whether differences in the expression of ACE2 and TMPRSS2 may explain why certain patients develop AP within minority groups. Further research into the biological mechanisms for assessing AP risk may provide additional insight into managing pancreatic injury in COVID-19 patients.

Lastly, large-scale studies are needed to assess the frequency of AP in COVID-19 patients. Most cases of AP have been reported in case reports and smaller retrospective studies. The lack of larger sample sizes and longitudinal studies provides a significant source of bias about these studies. Larger clinical studies reporting the ethnicities and drugs administered to these patients may provide insight into clinical management and risk factors for developing AP in COVID-19 patients.

Conclusion

The development of AP secondary to the SARS-CoV-2 virus remains a novel complication of COVID-19. However, the exact mechanism, fre-
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Frequency, and long-term effects of AP related to COVID-19 remain unknown due to a lack of larger retrospective studies [64]. Further preclinical and clinical analysis of autopsies and mouse model studies would provide insight into the pathogenesis of SARS-CoV-2 on the pancreas [64]. Additional studies on ACE2 and TMPRSS2 may improve understanding of the biological mechanisms and risk factors for AP with respect to ethnicity. Beyond AP, it remains to be seen whether pancreatic cancer patients will develop short- or long-term complications from COVID-19. Longitudinal studies of pancreatic cancer patients who contracted SARS-CoV-2 before or after starting chemotherapy may provide additional insight into managing complications within this patient population.

Disclosure of conflict of interest

None.

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References

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[27] Pezzilli R. Exocrine pancreas involvement in celiac disease: a review. Recent Pat Inflamm Allergy Drug Discov 2014; 8: 167-172.


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