COVID-19 and the Pancreas

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented, single-stranded, positive-sense RNA virus responsible for the 2019 coronavirus disease (COVID-19) [1]. Being highly pathogenic and contagious, COVID-19 spread throughout the world and was declared as a public health emergency of international concern [2]. Clinical manifestations of COVID-19 are heterogeneous, varying from asymptomatic disease to severe lung infection leading to acute respiratory distress syndrome (ARDS), multi-organ failure or even death [3].

Although SARS-CoV-2 primarily affects the respiratory tract causing influenza-like symptoms, such as cough, dyspnea or fever, evidence emphasize the role of the gastrointestinal system in the pathogenesis of the virus [4]. According to a recent meta-analysis, viral RNA in stool samples is detected in 54% of COVID-19 patients, while positive fecal testing appears to persist approximately 28 days after the onset of symptoms significantly exceeding the duration of viral presence in respiratory specimens [4]. Hence, the role of the fecal-oral route as an alternative but crucial mode of transmission is currently drawing research attention. Additionally, abnormal liver functions and digestive symptoms are documented in 19% and 15% of patients, respectively [4]. Consequently, the detrimental effects of SARS-CoV-2 on the hepatobiliary and the gastrointestinal system raise concerns about viral impact on pancreatic function.

However, only a limited number of studies have shed light on pancreatic function alterations in the course of SARS-CoV-2 infection. Notably, recent data support that pancreatic injury, as indicated by elevated levels of amylase and lipase, occurs in considerable rates [5,6]. The prevalence of increased pancreatic enzymes in hospitalized patients was estimated to be 17% by Wang et al [5]. In line with this, another single-center Chinese study demonstrated that 16% of patients with severe COVID-19 had elevated serum levels of both amylase and lipase [6]. More severe disease on admission and higher incidence of gastrointestinal symptoms were reported in cases where COVID-19 was accompanied by pancreatic injury. Moreover, concurrent liver function abnormalities with elevated aminotransferases and gamma-glutamyl transferase (γ-GT) and findings of immune system dysregulation with decreased CD3+ and CD4+ T-cells were observed [5].

Several studies have linked COVID-19 with the development of acute pancreatitis and, in certain cases, it has been described that COVID-19 mimics a pancreatitis-like clinical presentation with abdominal pain, loss of appetite and nausea as main symptoms [7-10]. Although gallstones and alcohol are the leading causes, viral-induced pancreatitis is a well-established entity principally triggered by mumps, Coxsackie, Epstein-Barr, Cytomegalovirus or other viral infections [11]. Due to absence of other etiologies, the temporal relationship between viral infection and acute pancreatitis supports a potential injurious effect of SARS-CoV-2 on pancreatic tissue [8-10]. Accordingly, mild to moderate lesions were recognized in 7.5% of COVID-19 patients during imaging evaluation [6]. Focal or diffused enlargement of pancreas and dilated pancreatic duct constituted the main radiological findings. [6,10].

SARS-CoV-2 shares 79% genetic similarity with severe acute respiratory syndrome coronavirus (SARS-CoV) and both viruses use the same protein to enter host cells. Human angiotensin-converting enzyme 2 (ACE2) has strong affinity with spike (S) protein, one structural

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protein of SARS-CoV-2, and operates as a receptor for viral binding to cells [12]. Given that ACE2 is expressed in pancreatic cells in abundance, a direct cytopathic effect of SAR-CoV-2 mediated by local viral replication may be hypothesized [6]. Correspondingly, post-mortem biopsies in SARS-CoV cases have detected viral particles in pancreatic tissue [13]. Furthermore, abnormal glucose levels have been described in severe COVID-19 patients without exposure to corticosteroids, resembling SARS-induced acute insulin dependent diabetes mellitus [5,14]. This might be attributed to high ACE2 expression in endocrine pancreatic cells implying viral-induced damage on islets of Langerhans [6].

Furthermore, pancreatic injury during COVID-19 might come as a result of an immune-mediated mechanism. Severe SARS-CoV-2 infection is followed by increased secretion of inflammatory cytokines (IL-1, IL-6, IL-10), lymphopenia with elevated neutrophil-to-lymphocyte ratio (NLR) and coagulation function derangement [3,15]. Exuberant inflammatory response and cytokine storm trigger various potential pathogenetic pathways of pancreatic damage, such as microcirculation disturbance, leukocyte excessive activation and complement cascade activation [16]. In addition, elevated pancreatic enzymes were more likely to appear in critically ill patients with a parallel dysfunction of other organs [5]. Therefore, pancreatic impairment may occur in the context of a dysregulated immune system causing a sequence of non-specific multi-organ complications.

Drug-induced pancreatic damage during hospitalization of COVID-19 cases cannot be excluded. Even though there is currently no effective treatment against SARS-CoV-2, a series of pharmaceutical agents are used according to ongoing treatment protocols for severely affected patients [17]. Specifically, antipyretics (acetaminophen), antibiotics (penicillins, quinolones, macrolides), colchicine, protease inhibitors (lopinavir/ritonavir) and other antivirals (remdesivir) are commonly administered drugs, which have been accused of inducing acute pancreatitis [16]. Thus, we should not overlook that critically ill patients with impaired pancreatic function might be more prone to a second "hit" on pancreatic cells driven by drug toxicity.

Whether altered pancreatic function mirrors an underlying occult or apparent chronic pancreatic disease remains unclarified. There is no evidence supporting that pancreatic diseases predispose individuals to SARS-CoV-2 infection but these patients are probably more susceptible to severe forms of COVID-19 depending on the extent of the pertinent immunological disarray. A recent meta-analysis reveals that diabetic populations with COVID-19 present increased rates of progression to ARDS and mortality, while this correlation is stronger in younger age groups [18]. Hence, chronic pancreatic disease or malignancy complicated by diabetes renders patients more vulnerable to COVID-19. Regarding cystic fibrosis, the propensity of this inherited genetic disorder to inflict pancreatic insufficiency and chronic pneumonia underscores the threat of a possible SARS-CoV-2 infection. A recent multi-center study including 40 individuals showed that cystic fibrosis does not influence the clinical course of COVID-19 [19]. Nevertheless, all patients with chronic pancreatic diseases are encouraged to strictly adhere to preventative measures.

Oncological patients who contract the novel coronavirus consist a per se risk group for severe COVID-19. Therefore, it is of vital importance to formulate guidelines to protect this vulnerable population from viral exposure as well as from disease progression due to testing or treatment delays. The European Society for Medical Oncology (ESMO) has launched recommendations regarding the prioritization of patients with pancreatic neoplasms [20]. In case of infection, corticosteroid dose adjustment to minimize immunosuppression, assessment of venous thromboembolism risk and individualized approach are indicated [20].

In conclusion, even though acute pancreatitis is an atypical manifestation of SARS-CoV-2 infection, mild pancreatic function derangement of unresolved pathophysiology is possible, particularly in severely affected patients. Either a direct viral-induced cytopathic effect or an indirect mechanism associated with hyper-inflammatory response and drug toxicity might engender pancreatic injury during COVID-19. Monitoring of pancreatic enzymes is suggested in patients with underlying pancreatic disease or preeminent gastrointestinal symptoms in order to identify early damage, which potentially aggravates systematic inflammation and contributes to progression to ARDS. Further studies are needed to clarify the relationship between COVID-19 and pancreatic injury.

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