Letter to the Editor

Could immune activation cause pancreatitis in COVID-19 patients?

Gabriela Gama Freire Alberca^, Naiane Samira Souza Cardoso^, Ricardo Wesley Alberca^

Laboratorio de Dermatologia e Imunodeficiencias (LIM-56), Departamento de Dermatologia, Instituto de Medicina Tropical, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Correspondence to: Dr. Ricardo Wesley Alberca. Departamento de Dermatologia, Faculdade de Medicina FMUSP, Laboratorio de Dermatologia e Imunodeficiencias (LIM-56), Universidade de Sao Paulo, Av. Dr. Enéas Carvalho de Aguiar, 470, São Paulo 05403-000, Brazil.
Email: ricardowesley@usp.br.

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We read with really great interest the paper published by Gadiparthi *et al.* entitled "*Acute pancreatitis in a patient with COVID-19: a case report*" in *Translational Gastroenterology and Hepatology* (1). The authors presented a case of elderly, with type 2 diabetes mellitus (T2DM), infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that developed pancreatic injury (1). We would like to add a few points for consideration.

Although is possible that a direct SARS-CoV-2 infection occurs in the pancreas, due to the expression of the SARS-CoV-2 entry's receptor angiotensin-converting enzyme 2 (ACE 2) receptor. We would like to discuss how the immune response to SARS-CoV-2 could contribute to the development of pancreatitis in coronavirus disease 2019 (COVID-19).

Tumor necrosis factor (TNF) is increased in COVID-19 patients and increases further in T2DM severe COVID-19 patients, this cytokine is associated with both the induction of necroptosis and apoptosis in experimental pancreatitis models (2). TNF has a central role in pancreatitis, as treatment with monoclonal TNF antibody (infliximab) can reduce the parenchymal inflammation and tissue necrosis pancreas (3).

In fact a major feature in pancreatitis is the cellular death by either apoptosis or necroptosis, that could be stimulated or influenced by the severe cytokine storm and inflammatory mediators, produced during COVID-19 (4).

Additionally, COVID-19 patients can develop a gastrointestinal dysbiosis (5), which can increase gastrointestinal permeability, causing bacteria translocation and induce immune activation in the pancreas via toll-like receptors and/or NOD-like receptor family pyrin domain containing-3 (NLRP3) inflammasome (6). The NLRP3 inflammasome lead to the secretion of interleukin (IL)-1β, IL-18 and the induction of pyroptosis cell death (6). Further increasing the overall inflammation in COVID-19.

Interestingly, pancreatitis may also increase the gut permeability allowing bacterial translocation, providing a sub sequential local and systemic inflammatory stimulus, that may development into multi-organ damage, and endotoxemia (7).

In addition, pathogen-associated molecular patterns (PAMPs) from the gastrointestinal tract or the damage-associated molecular patterns (DAMPs) from the pancreatic cell death may induce the migration of neutrophils and the generation of local neutrophil-extracellular traps (NETs) (8). Importantly, the induction of NETs may also activate trypsinogen in pancreatic cells, further contributing to pancreas inflammation, induction, and the release of DAMPs (8). Generating a pro-inflammatory loop in the pancreas. Especially in COVID-19 patients that already have an increase in circulating neutrophils.

The recognition of PAMPs or DAMPs via pattern recognition receptors (PRR) can lead to myeloid differentiation primary response gene 88 (MyD88) signaling or TIR-domain-containing adapter-inducing interferon-β (TRIF) signaling resulting in Factor nuclear

^ ORCID: Gabriela Gama Freire Alberca, 0000-0002-3467-5562; Naiane Samira Souza Cardoso, 0000-0002-3305-6567; Ricardo Wesley Alberca, 0000-0002-3602-3306.

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kappa B (NF-κB) activation in pancreatic acinar cells, which may progress to pancreatitis and also the development of cancer (4). Therefore, long-term follow-up on COVID-19 patients should be performed to assess the risk for pancreas-associated comorbidities.

NF-κB activation can lead to the activation of the signal transducer and activator of transcription (STAT)3 and STAT1, and the production of more pro-inflammatory mediators such as IL-6, chemokine (C-C motif) ligand 2 (CCL2), and interferons, that lead to the infiltration of monocytes and T helper (Th) cells. COVID-19 patients commonly present lymphopenia and a deficiency in the regulatory immune response (9), which may also aggravate the pancreas lesion and or fibrosis (10).

In summary, SARS-CoV-2 can infect directly pancreas cells, but the immune activation during COVID-19 also represents a risk for the development of pancreatitis. In this light, further investigations on convalescent COVID-19 patients should assess the pancreas and the risk for pancreas-associated comorbidities.

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