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Emerging Phenotype of Severe Acute Respiratory Syndrome-Coronavirus 2–associated Pancreatitis

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As the global pandemic of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) continues, nuances of the disease it precipitates in humans continue to emerge. After early reports of presentation with gastrointestinal-type symptoms in China[1] and Italy,[2] a group from Wuhan reported a series of 9 patients with purported pancreatic injury in the context of SARS-CoV2 infection[3] but did not provide robust evidence for pancreatitis. relying on mild hyperamylasemia alone. Current international consensus for a diagnosis of acute pancreatitis requires 2 of the following 3 features: abdominal pain consistent with pancreatitis, serum amylase/lipase greater than 3 times the upper limit of normal, and characteristic findings on cross-sectional imaging.[4] Simply put, there are too many causes for hyperamylasemia in the context of systemic illness, with or without SARS-CoV2, for its use in isolation as a marker of pancreatic injury. Nonetheless, we report here 5 cases of atypical but proven acute pancreatitis in the context of SARS-CoV2 infection.

Methods

This review was registered with the Liverpool University Hospitals NHS Foundation Trust audit department (ID TA0002744). Cases were identified by searching admission diagnoses (International Classification of Diseases, 10th revision code K85) or radiology requests and reports for "acute pancreatitis."

SARS-CoV2 was diagnosed when either swabs were positive on rapid polymerase chain reaction (VIASURE, Certest Biotec, Spain) or patients had radiologic evidence of SARS-CoV2 infection (Supplementary Figure 1). Cases with pre-existing pancreatic pathology or where the etiology was clearly non–SARS-CoV2 related were excluded.

Data extracted from patient and radiology records were used to calculate clinical scores and hepatic steatosis estimates by analysis of contrast-enhanced computed tomography (CECT) images as previously described.[5] Imaging findings were re-reported by an expert pancreatic radiologist.

Results

Between March 14, 2020 and April 30, 2020, 35 patients with acute pancreatitis were assessed at the Royal Liverpool University Hospital. Twenty-five patients were negative for SARS-CoV2 and were excluded. Of the remaining 10 patients who were deemed positive for SARS-CoV2, a further 5 were excluded because they presented with a clearly defined etiology (eg, choledocholithiasis). The remaining 5 patients, all with SARS-CoV2, presented atypically yet homogenously with a distinct metabolic-pancreatitis phenotype. These 5 patients form the cohort subsequently discussed (Supplementary Figure 1).

All 5 patients (Table 1) were young adult men (median age, 42 years; interquartile range [IQR], 15) who were either overweight or obese (median body mass index, 30 kg/m^2; IQR, 6.7). Serum amylase was elevated but nondiagnostic in all patients (median, 149 U/L; IQR, 238), and abdominal CECT was used to confirm the diagnosis. Patients had no sonographic evidence of gallstones on this admission. No patient had known cardiovascular disease. On admission patients had evidence of metabolic distress; median levels of triglycerides and glucose were 2.7 mmol/L (IQR, 18.2) and 10 mmol/L (IQR, 8.6), respectively. One patient had sustained ethanol use without hypertriglyceridemia or hyperglycemia but importantly had no prior pancreas symptoms. One patient had a long-term medication history (atorvastatin and sertraline), again without prior pancreatitis symptoms. However, in all patients CECT showed transient moderate to severe hepatic steatosis (<104 Hounsfield units), which rapidly regressed in patients for whom follow-up CECT was available. Median attenuation on admission was −3.5 Hounsfield units (IQR, 55.8) with a median improvement at 7 days of 31.12 Hounsfield units (IQR, 3.1). The pattern of pancreatic inflammation was similarly unusual in these patients: mild pancreatic edema without significant pancreatic or peripancreatic necrosis, with distinct duodenal/periduodenal inflammation involving the second and third part of the duodenum. Radiologic findings were accompanied by a profound systemic inflammatory response (SIRS, [1-2 criteria on admission; 2-4 after 48 hours]) and dramatic elevation of C-reactive protein

Abbreviations used in this paper: CECT, contrast-enhanced computed tomography; IQR, interquartile range; SARS-CoV2, severe acute respiratory syndrome-coronavirus 2.

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Table 1. Clinical Characteristics of Patients With Acute Pancreatitis in the Context of Coronavirus Disease 2019 Infection

	Patient					Summary Statistic	
Characteristic	1	2	3	4	5	Median	Interquartile Range
Demographics							
Age, *y*	29	41	42	47	53	42	15
Sex	M	M	M	M	M		
Body mass index, kg/m^2	32.9	35.8	29.7	25.7	30	30	6.7
Ethnicity	Other Asian	White British	White British	White British	Other White		
Hypertension	No	No	No	No	No		
Diabetes mellitus	No	No	No	No	No		
RespiratoryDisease	No	No	Asthma	No	No		
Charlson comorbidity index	0	0	0	0	1		
Coronavirus disease 2019 status							
Computed tomography score	Normal (CVCT0)	Classic/probable (CVCT1)	Classic/probable (CVCT1)	Non–coronavirus disease 2019 (CVCT3)	Classic/probable (CVCT1)		
Throat swab	Positive	Negative	Unknown	Positive	Negative		
Pancreatitis diagnostics							
Typical pain	Yes	Yes	Yes	Yes	Yes		
Amylase, *U/L*	77	149	378	211	36	149	238
Amylase timing (hours after pain)	27	20	6	16	23	20	14
Computed tomography on admission	Pancreatitis	Pancreatitis	Pancreatitis	Pancreatitis	Pancreatitis		
Pancreatitis risk factors							
Gallstones on ultrasound (Ultrasound)	No	No	No	No	No		
Alcohol intake, *g/wk*	0	80	400	50	0	50	240
Smoker	Never	Yes	Never	Ex	Yes		
Medication	None	None	Omeprazole; thiamine; hydroxycobalamin	Atorvastatin; sertraline	None		
Clinical characteristics of pancreatitis							
SIRS (admission)	2	2	1	2	2		
SIRS (48-h peak)	4	2	3	4	2		
CRP (admission)	258	37	5	8	31	31	141
CRP (peak)	597	550	292	485	282	485	286.5
Peak CRP time, *days from admission*	0	2	9	2	0	2	5.5
Organ failure	No	No	No	No	No		
Activity index (admission)	250	220	—	245	145	232.5	85
Activity index (48 h)	205	150	—	175	25	162.5	141.3
Imaging findings							
Focus of inflammation	Periduodenal (D1-D4) and pancreatic head	Periduodenal (D2-D3) and pancreatic head	Periduodenal (D1-D3) and peripancreatic	Duodenal thickening (D2-D3) and peripancreatic	Duodenum spared; peripancreatic		
Peripancreatic necrosis	No	No	No	No	No		

Table 1. Continued

Characteristic	Patient 1	2	3	4	5	Summary Statistic Median	Interquartile Range
Pancreatic necrosis	None	None	None	Pancreatic tail (<30%)	None		
Acute fluid collections	Paraduodenal	None	Peripancreatic	Pancreatic tail	Paraduodenal		
Modified Balthasar score	6	2	4	8	4	4	4
Metabolic parameters							
New-onset diabetes	Yes	Yes	No	No	Yes		
Glucose on admission, *mmol/L; mg/dL*	14.3; 257.4	16.6; 298.8	7.9; 142.2	5.9; 106.2	10; 180	10; 180	8.6; 154.8
HbA_{1c}, *IFCC mmol/mol*	86	—	—	36	47		
Urinalysis on admission	Glucose 4+	Glucose +; ketones +	—	—	—		
Insulin therapy	Yes	Yes	No	No	No		
Triglycerides on admission, *mmol/L; mg/L*	30.9; 2740	8.4; 743	1.65; 146	2.7; 239	1.3; 115	2.7; 239	18.2; 1610
Hepatic steatosis (admission), *HU*	18.0	–46.7	–18.1	11.1	—	–3.5	55.8
Hepatic steatosis (7 days), *HU*	50.6	–15.6	8.30	42.2	—	25.2	50.1
ΔHepatic steatosis	32.7	31.1	26.4	31.1	—	31.1	3.1
Outcome parameters							
Severity of pancreatitis	Moderate	Moderate	Moderate	Moderate	Moderate		
Length of stay, *days*	16	14	16	12	6	14	7
Intervention	No	No	No	No	No		
New therapy on discharge	Insulin; PERT; fibrate	Insulin	No	PERT; fibrate	No		

NOTE. Ethnicity labels are those used by the Office of National Statistics of the United Kingdom. Coronavirus disease 2019 computed tomography score is based on the British Society of Thoracic Imaging criteria where changes are classed as "probable" when there is >70% confidence of coronavirus disease 2019 infection. Systemic inflammatory response syndrome (SIRS) score is calculated by presence of the following: temperature > 38°C or <36°C, heart rate > 90 bpm, respiratory rate > 20 or $Paco_2$ < 32 mm Hg, and white blood cell count > 12,000/mm^3. Organ failure is defined as a Sequential Oran Failure Assessment score of 2 or more. Pancreatic activity index is a composite score including organ failure, tolerance to oral diet, SIRS, abdominal pain, and intravenous morphine equivalent dose on any given day. Hepatic steatosis is based on CECT image evaluation as previously reported. Severity of pancreatitis is defined by the Revised Atlanta Classification 2012. CRP, C-reactive protein; CVCT, corona virus CT score; HU, Hounsfield unit; IFCC, International Federation of Clinical Chemistry.

(median, 31 mg/L [IQR, 141] on admission vs 485 mg/L [IQR, 286.5] after 48 hours).

All patients were treated with intravenous fluids; 3 of 5 received insulin and/or fibrate therapy. Abdominal pain was managed with opiate analgesia, and all patients tolerated an oral diet from admission. Four of 5 patients with CT findings suggestive of pneumonitis received broad-spectrum intravenous antibiotics. None of the patients received corticosteroids, and none required organ support, beyond low-flow oxygen, or admission to a level 2/3 care setting. Thus, all were classed as moderate pancreatitis based on the presence of acute fluid collections alone. Two patients required pancreatic enzyme replacement therapy to control their abdominal pain and steatorrhea, indicating a true exocrine component to their disease. Median length of stay was 14 days (range, 6-16).

Discussion

Despite the dramatic way these 5 patients presented, with multiple metrics predictive of severe disease, their pathway was much more benign than anticipated and not dissimilar from a typical attack of moderate pancreatitis. We therefore propose the combination of male sex, abdominal pain, metabolic stress, and CT findings of predominantly pancreaticoduodenal inflammation with steatosis represent a distinct subset of pancreatitis in patients infected with SARS-CoV2. Furthermore, we postulate that the endocrine pancreas is particularly vulnerable to this infection. Although we cannot deduce causality based on data presented here, we note that the human pancreas is known to express high concentrations of angiotensin-converting enzyme 2,[6] especially (but not exclusively) in the pancreatic islets where binding to SARS-CoV1 has been shown to

induce acute diabetes.[7] Persons with pre-existing metabolic syndrome, even if not formally diagnosed, may be at particular risk in light of the high body mass indices and HbA_{1c} in our case series.

Acute pancreatitis secondary to hypertriglyceridemia is uncommon in Western populations and is more often associated with severe disease, organ failure, and death than other etiologies.[8] No patient presented here had transient or persistent organ failure, and the main reason for the prolonged length of stay in all cases was poor diabetic control or persistent elevation of serum inflammatory markers. We speculate that because of the low levels of free pancreatic enzymes (as evidenced by near-normal levels of circulating pancreatic amylase), toxic lipolysis does not occur, and the liver is able to absorb most triglycerides resulting in the changes in hepatic steatosis observed. These patients likely represent the severe end of the pancreatopathy spectrum, but transient dyslipidemias and impaired glucose tolerance may be common in SARS-CoV2 patients and warrant further investigation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.069.

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