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Case report

COVID-19 associated pancreatitis: A mini case-series

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A R T I C L E I N F O

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A B S T R A C T

Introduction: One of the recognized causes of acute pancreatitis is viral-induced pancreatitis. The SARS-COV-2 virus has been linked to pancreatic injury and hence the causation of acute pancreatitis. This paper reports three cases of acute pancreatitis linked to COVID-19 infection adding to serving to further consolidate evidence.
Case presentation: Three patients aged between 63 and 87 years were diagnosed with acute pancreatitis and concomitant or previous COVID-19 infection. Criteria for diagnosis of pancreatitis were according to the revised Atlanta criteria. None of the patients had had previous episodes of pancreatitis and other aetiologies were not suggestive. The patients were not vaccinated against SARS-CoV-2. Supportive treatment was instituted for the three patients, and all made an uneventful recovery. Mean hospital stay was 4 days.
Discussion: The diagnosis of acute pancreatitis in the presented cases is being linked to COVID-19 infection, as other causes were not evident. There is however a confounding factor, as the patient in case 2 had slightly elevated triglyceride levels and had been on long-term low dose atorvastatin, both of which are associated with a low risk of acute pancreatitis. However, she had never had pancreatitis prior to this presentation.
Conclusion: The novel virus SARS-COV-2 has also been linked to pancreatic damage and thus a possible causative factor in acute pancreatitis. This mini-case series presents three cases of acute pancreatitis in COVID-19 positive patients, in the absence of other risk factors. This phenomenon linking COVID-19 and pancreatitis has been expounded by other case reports and cohort studies from around the world. It is reasonable to acknowledge that, like other viruses, SARS CoV-2 may cause acute pancreatitis, although sounder evidence from the international community needs to be compiled.

1. Introduction

Most patients with COVID-19 infection present with respiratory symptoms, however gastrointestinal symptoms have also been reported. Cheung et al. [1] conducted a systematic review and meta-analysis that reported gastrointestinal symptoms in up to 17.6% of patients diagnosed with COVID-19. Case reports [2,3,4] and retrospective cohort studies [5] have reported a link between COVID-19 and acute pancreatitis. The first to describe this were Wang et al. [6], who published a case series of 52 patients, out of which 9 were diagnosed with acute pancreatitis. However, it is important to note that their definition of pancreatic injury consisted of elevated amylase or lipase. Different definitions of acute pancreatitis in subsequent studies make it difficult to draw firm conclusions on the causality between SARS-CoV-2 infection and pancreatitis [7]. In light of this, Bonney et al. [8], identified an urgent need for increased international collaboration to gather scientific and clinical experience about COVID-19 associated pancreatitis, to improve understanding of the disease and its management, and ultimately, patient outcomes. This mini-series presents three cases of acute pancreatitis in patients with previous or concomitant COVID-19 infection.

2. Method

These cases were gathered over a one-year period between March 2020 and March 2021 and treated at Mater Dei Hospital in Malta and Gozo General Hospital. Cases were collected during this time period as the first COVID-19 case in Malta was recorded in March 2020, despite the pandemic starting in December 2019 in other parts of the world.

Collected data were retrieved from patient's records, discharge letters, iSOFT Clinical Manager (iCM) and the local surgical department handover document. Consent was obtained from patients and their relatives where the patient was unable to give consent. This mini case-series has been reported in line with the PROCESS guidelines [9].

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3. Case 1

A 63-year-old lady presented to the emergency department with a 1-day history of intermittent epigastric pain. Patient was nauseous but denied vomiting and other gastrointestinal symptoms. She also denied alcohol intake and was a non-smoker. A week earlier she had tested positive for COVID-19 infection. At the time of presentation, she denied respiratory symptoms. Her past medical and surgical history included diabetes mellitus, hypertension and Whipple's procedure for ampullary tumour.

On physical examination she was afebrile and vital parameters were within normal limits. On examination of her abdomen there was epigastric tenderness but no rebound or guarding, along with mild suprapubic tenderness. Her laboratory results showed elevated serum amylase (1079 U/L), white cell count (WCC) of 4.13×10^9/L, a haemoglobin level of 13.8 g/dL, and a C-reactive protein (CRP) of 3 mg/L on admission. Her liver function tests were within normal ranges. Blood glucose levels were not checked. A repeat nasopharyngeal COVID-19 PCR swab confirmed presence of COVID-19. A chest X-ray was performed and showed no abnormalities (Fig. 1).

Based on her clinical presentation and laboratory investigations she was diagnosed with acute pancreatitis. She was resuscitated with IV fluids and an oral fat free diet was re-introduced slowly. She improved gradually on conservative and supportive management and made an uneventful recovery. A repeat COVID swab prior to discharge was not taken and the patient was required to self-isolate for a total of 14 days from diagnosis. Total inpatient stay was 4 days.

The patient was followed up on an outpatient basis. She recovered well post COVID-19 infection. A CT pancreas was performed 6 months after the acute presentation and showed status post Whipple's procedure and no evidence of tumour recurrence or any other abdominal pathology related to the causation of pancreatitis.

4. Case 2

An 87-year-old lady, was referred by a physician to the emergency department with generalized abdominal pain and suprapubic tenderness, associated with nausea and two episodes of vomiting (gastric contents). She was in a quarantine hospital as two weeks prior to this presentation she had tested positive for COVID-19 on nasopharyngeal swab PCR. She had tested negative for COVID-19 2 days prior to presentation.

She had been largely asymptomatic except for a sore throat. She was started on co-amoxiclav and clarithromycin by the physician for chest crepitations and this was subsequently changed to tazocin as her inflammatory markers were progressively increasing. Her past medical and surgical history included atrial fibrillation, congestive heart failure, hypertension, hyperlipidaemia (on low dose atorvastatin), dementia, diverticular disease and cholecystectomy.

On physical examination her abdomen was soft, tender in the

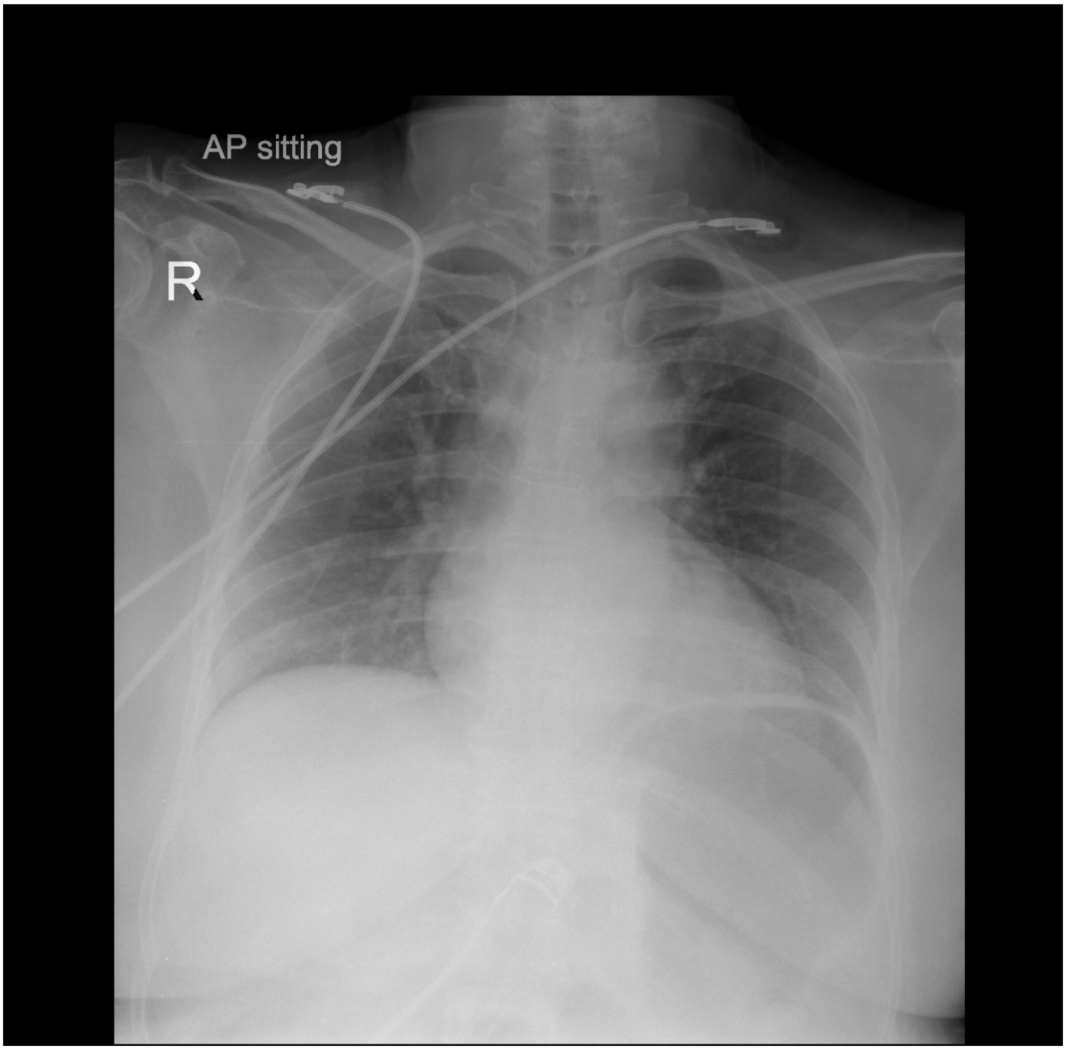

Fig. 1. An anteroposterior chest x-ray of the patient in case 1 showing no significant chest pathology.

epigastrium and left upper quadrant. On auscultation of the chest bibasal crepitations were present. The patient was afebrile and haemodynamically stable. Blood glucose was 10.4. Her laboratory investigations showed an elevated serum amylase of 499 U/L, a neutrophilia of 25 $\times$ 10^9/L, a raised CRP of 128 mg/L and a lactate dehydrogenase (LDH) of 231 U/L. Liver function tests were within normal ranges. Her triglyceride levels were slightly elevated at 2.24 mmol/L (upper limit 2.2 mmol/L). A computed tomography (CT) scan of the abdomen and pelvis confirmed acute pancreatitis (Fig. 2) and fibrotic changes in the lung bases bilaterally (Fig. 3). The lung changes were present on a CT scan done the year before. COVID-19 swab on admission was negative.

A urinary catheter was inserted and 700 mL of residual were recorded, hence she was diagnosed with acute urinary retention. She was treated conservatively with intravenous fluids and slow reintroduction of oral diet and made an uneventful recovery. A COVID-19 nasopharyngeal swab was taken prior to discharge and resulted negative. Upon discharge the patient was not required to quarantine as she had completed her quarantine one day prior to admission and had had two subsequent negative PCR swabs. Total inpatient stay was 5 days.

The patient was hospitalized again a few months later under the physicians with general health deterioration and an MRCP was performed. It showed status post-cholecystectomy and no stones in the biliary tree.

5. Case 3

A 64-year-old lady presented with a few hours' history of severe epigastric pain radiating to the back, associated with nausea and one episode of vomiting gastric contents. She denied lower urinary tract symptoms and change in bowel habits. No respiratory symptoms were present. This was the first episode of its kind. Her past medical history included gastro-oesophageal reflux disease, hypertension and anxiety.

On examination she was afebrile, tachycardic with a heart rate of 110 bpm but normotensive. Her pulse oximetry readings were 99% on air. Blood glucose was 9.1. On palpation her abdomen was soft but tender in the epigastrium, with no rebound or guarding. Laboratory investigations showed an elevated serum amylase of 2141 U/L, a neutrophilia of 15 $\times$ 10^9/L, a haemoglobin of 13.1 g/dL, CRP of 5 mg/L and LDH 182 U/L. Her liver function tests were deranged (ALT 107 U/L, gamma-GT 403 U/L and bilirubin 8 U/L). Lactate was slightly high at 2.5. A CT scan of the abdomen and pelvis showed small peripancreatic fat stranding due to acute interstitial pancreatitis (Fig. 4). There were few atelectasis at the right lung base on CT abdomen and pelvis (Fig. 5) but otherwise no features of COVID-19 pneumonia were seen on CT scan. A CT thorax was not performed.

A routine screening COVID-19 nasopharyngeal swab was taken on admission and resulted positive. The patient was admitted for conservative and supportive management of acute pancreatitis. The patient never developed any symptoms related to COVID-19. A COVID-19 nasopharyngeal swab was taken prior to discharge and was negative. The patient made an uneventful recovery and was discharged after 3 days, requiring a quarantine of 14 days from the day of diagnosis.

The lady was seen at an outpatient clinic four months later. An ultrasound of her abdomen and pelvis was performed and showed no gallstones.

6. Discussion

Cholelithiasis and alcohol consumption are leading causes of acute pancreatitis. Viral pancreatitis secondary to Epstein-Barr virus, Hepatitis-A virus, mumps, measles and coxsackie has been well described in the literature [10,11]. Emerging literature suggests that the pancreas may be a target organ for COVID-19 infection, resulting in

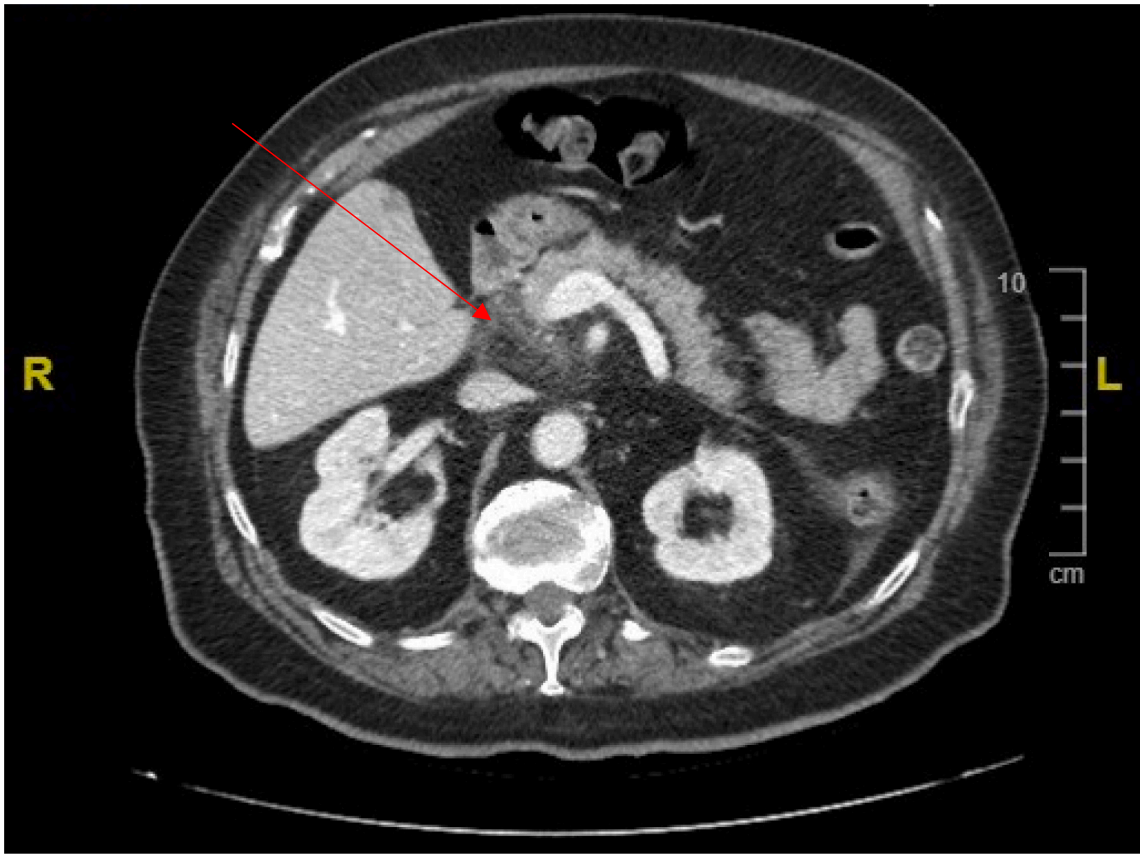

Fig. 2. CT scan showing fat stranding around the head of pancreas and in the pancreaticoduodenal groove consistent with acute pancreatitis.

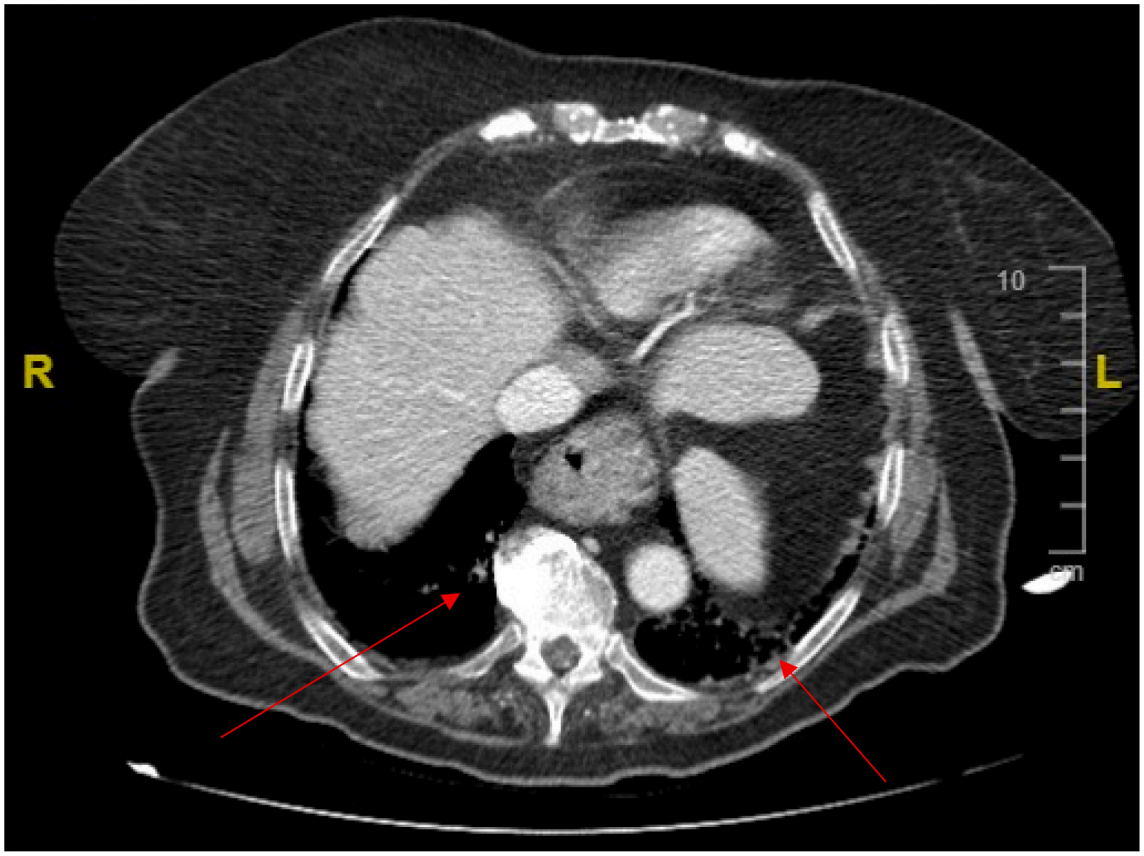

Fig. 3. CT abdomen and pelvis showing fibrotic changes in lung bases.

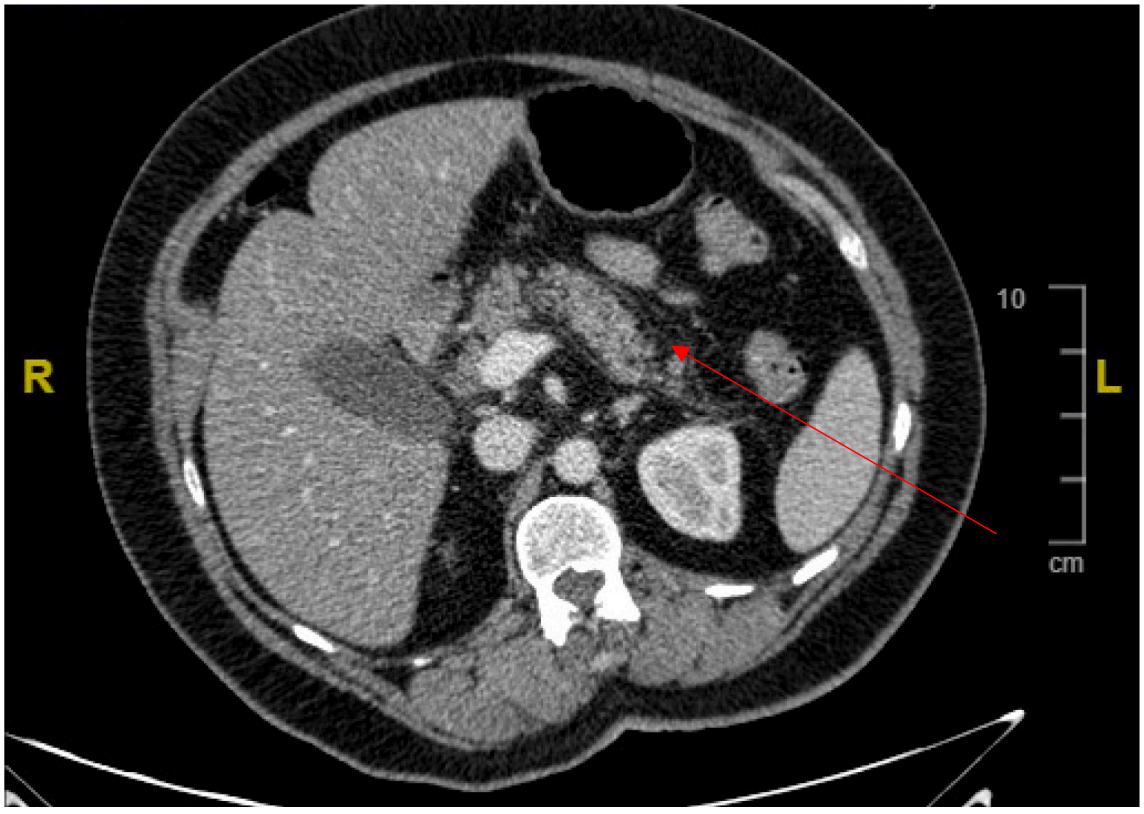

Fig. 4. CT scan showing a small amount of peripancreatic fat stranding due to acute interstitial pancreatitis.

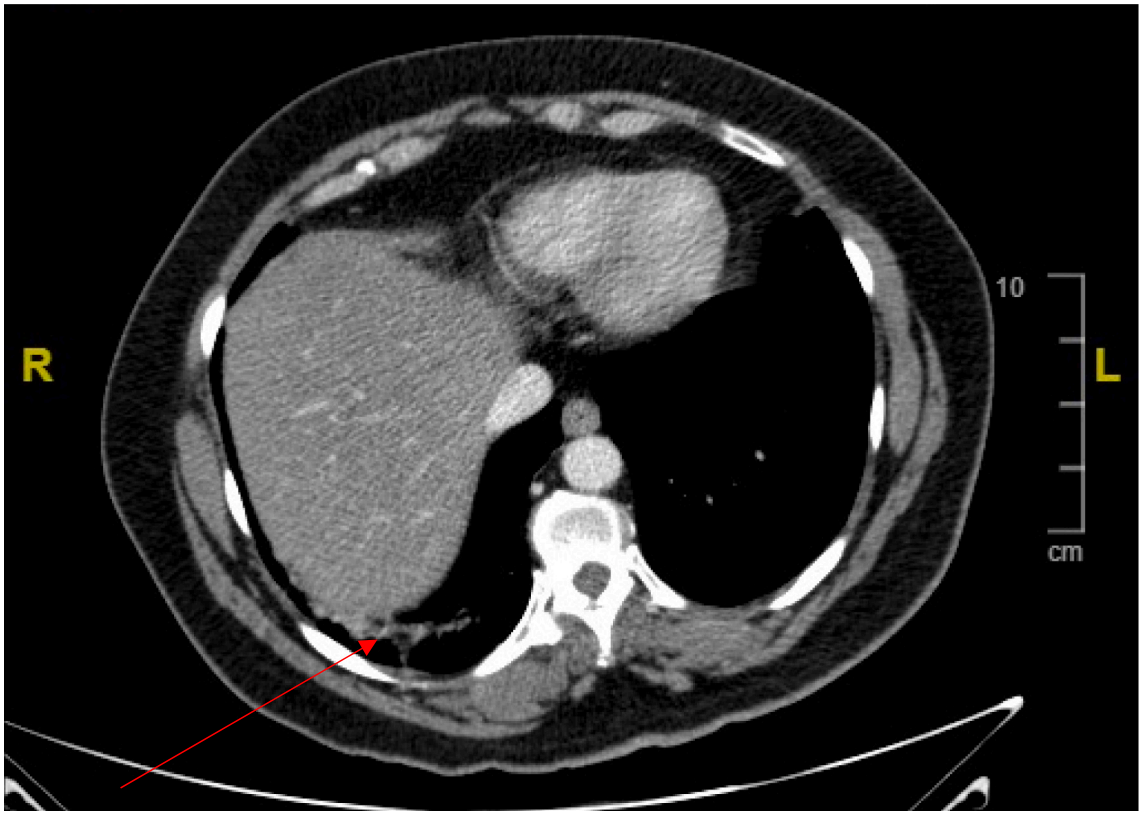

Fig. 5. CT scan showing few right basal atelectasis in a COVID-19 positive patient without respiratory symptoms.

acute pancreatitis with possibly increased severity. The pathogenesis of COVID-19 is thought to be mediated by angiotensin converting enzyme-2 (ACE-2) receptor, which is found on the cell surface and acts as a viral receptor for entry into the host's cells. ACE-2 receptors are highly expressed in pancreatic cells [2].

A 17% incidence of pancreatic injury was reported by Wang et al. in a case series of 52 patients suffering from COVID-19 infection. Liu et al. [12], also claimed 17% incidence of pancreatic injury in a study of 67 patients with COVID-19 infection. However, one should note that serum markers were mildly elevated, and abdominal pain was not reported in any of the two studies. In Liu et al.'s study [12], only 7.64% of patients showed radiological evidence of pancreatic injury on CT scan. According to the revised Atlanta classification system, acute pancreatitis is defined as the presence of any 2 of the following 3 criteria: 1) abdominal pain, most often acute onset severe epigastric pain, 2) increased serum amylase or lipase levels greater than 3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan [3].

All the 3 cases presented here satisfy at least two of the criteria, since they all presented with acute abdominal pain and elevated serum amylase. Cases 2 and 3 both had their diagnosis confirmed on CT. Cholelithiasis, alcohol intake and other causes of acute pancreatitis were excluded; here one is obliged to mention that Case 2 had mildly raised triglyceride levels (2.24 mmol/L) and was on atorvastatin. Of particular interest is that both case 1 and 2 developed abdominal symptoms after respiratory symptoms and their initial COVID-19 diagnosis. This is similar to most case reports published about COVID-19 associated pancreatitis. Given the temporal dissociation between initial respiratory symptoms and pancreatitis, in such cases, pancreatic injury is thought to be secondary to an immune mediated inflammatory response, rather than direct virus injury on the pancreas [13].

This contrasts with case 3, where the presenting symptom was acute severe epigastric pain, without any respiratory symptoms. Kandasamy [2] published a similar atypical case of a patient who presented with gastrointestinal symptoms and a raised amylase in the absence of respiratory symptoms. Acute pancreatitis was also radiologically confirmed on CT scan. Aloysius et al. [14], also published a similar case. In the absence of temporal dissociation, pancreatic injury in case 3 may be due to direct viral injury. This is significant because it implies that acute pancreatitis may be the first presenting symptom of SARS-CoV-2 infection, hence one should be vigilant in screening for COVID-19 infection in the presence of gastrointestinal symptoms.

The COVID PAN collaborate study investigated the severity and outcomes of COVID-19 associated pancreatitis. They concluded that in concomitant COVID-19 infection and acute pancreatitis there is a higher risk of increased severity, poorer outcomes, prolonged duration of hospital stay and increased 30-day mortality [5]. The above three patients all made an uneventful recovery with a mean inpatient hospital stay of 4 days.

This case series is not without its limitations. These include the utilisation of serum amylase rather lipase as a marker of acute pancreatitis. Serum amylase has a lower specificity for acute pancreatitis than lipase, however serum lipase testing is not available in the Maltese Islands. Case 2 may have confounding aetiologies contributing to pancreatitis due to hypertriglyceridaemia and statins. Although these factors might contribute to acute pancreatitis, the triglyceride levels were only very mildly elevated by 0.02 mmol/L and the statin dose is classified as moderate intensity. Although US and CT scans were performed, only the patient in case 2 had a magnetic resonance cholangiopancreatography (MRCP) which is a more sensitive test for microlithiasis.

Currently the evidence linking SARS-CoV-2 to pancreatitis is equivocal. There has been sound evidence that the virus affects multiple organs including the pancreas but not necessarily causing acute pancreatitis [15]. Moreover, amylase and lipase may be high in COVID-19 in the absence of pancreatitis as suggested by de Madaria et al. [16]. The same authors suggested that diagnosis of acute pancreatitis in patients with COVID-19 infection should be based on imaging rather than

elevated pancreatic enzyme levels. This case series presents both serology, imaging and clinical features in the diagnosis of acute pancreatitis.

7. Conclusion

It is a widely accepted phenomenon that viruses such as human immune-deficiency virus (HIV), varicella zoster virus (VZV) and coxsackie contribute to the aetiology of pancreatitis, despite cholelithiasis and alcohol consumption being the most common factors [14]. The novel virus SARS-COV-2 has also been linked to pancreatic damage [2] and thus a possible causative factor in acute pancreatitis. This mini-case series does not rely on one aspect in diagnosing pancreatitis but on clinical features, imaging and serology making a stronger case for the diagnosis of pancreatitis in COVID-19 infection.

This phenomenon linking COVID-19 and pancreatitis has been expounded by other case reports [2,3,4] and cohort studies [5] from around the world. It is reasonable to acknowledge that, like other viruses, SARS CoV-2 may cause acute pancreatitis, although sounder evidence from the international community needs to be compiled [7].

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Ethical approval

Consent was obtained from the patients or their relatives when the patient was unable to give consent.

Written consent

Written informed consent was obtained from the patient or next of kin where the patient was unable to give consent, for publication of this mini case-series and accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal upon request.

Research registration

Not applicable.

Guarantor

Ms. Jessica Schembri Higgans, Ms. Sarah Bowman, Mr. Jo-Etienne Abela.

Provenance and peer review

Not commissioned, externally peer reviewed.

CRediT authorship contribution statement

Jessica Schembri Higgans: conceptualisation, methodology, investigation, writing original draft, visualisation.

Sarah Bowman: conceptualisation, methodology, investigation, writing original draft, visualisation, writing review and editing.

Jo-Etienne Abela: conceptualisation, methodology, writing review and editing, supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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