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Journal of Pediatric Surgery Case Reports 82 (2022) 102289

Contents lists available at ScienceDirect

Journal of Pediatric Surgery Case Reports

journal homepage: www.elsevier.com/locate/epsc

Lethal hemorrhagic necrotizing pancreatitis in a child with congenital immunodeficiency and COVID-19

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ARTICLE INFO

Keywords:
SARS-CoV-2
Necrotising pancreatitis
COVID-19

ABSTRACT

Purpose: Various manifestations of coronavirus (SARS-CoV-2) have been reported since the pandemic began. Some articles have reported acute pancreatitis in adult patients due to COVID-19 infection. To our knowledge this is the first report of acute hemorrhagic necrotizing pancreatitis in children associated with SARS-CoV-2 infection.

Case presentation: A 7-year-old girl with congenital immunodeficiency was referred to the intensive care (ICU) unit with acute respiratory distress syndrome. She required mechanical ventilation (MV) due to pulmonary involvement of COVID-19 (chest CT with lower lung ground-glass opacities). SARS-CoV-2 infection was laboratory confirmed. Following a 49-day stay in the ICU, due to the clinical and radiological signs of acute abdomen and to the rapid deterioration in the clinical status, an indication to proceed an urgent surgerical intervention was made. Intraoperatively an adhesiolysis with blunt dissection of the of gastrocolic ligament was performed, then followed by debridement of the necrotic pancreas (more than 1⁄2 of the pancreas was damaged). Continuous lavage and drainage were placed. During the post-operative period, patient required aggressive MV and insulin therapy for persistent hyperglycemia. The CT scans reported a necrosis of the pancreas and we observed amylase and lipase elevation in the peritoneal lavage sample. Despite active intensive therapy, the patient's condition did not improve and she died 38 days after laparotomy as a result of multi-organ failure.

Conclusion: The mechanism for the development of acute haemorrhagic necrotizing pancreatitis in the COVID-19 positive patients is unclear; perhaps it is due to a direct cytopathic effect from the COVID-19 virus, or due to the ACE2 expression in pancreas.

1. Introduction

In general, children with COVID-19 infection present with milder symptoms and are at lower risk of hospitalization and life-threatening complications compared to adult patients. Children with severe COVID-19 infection may develop neurologic manifestations and occasionally acute disseminated encephalomyelitis, acute transverse myelitis, respiratory failure, myocarditis, shock, ocular

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https://doi.org/10.1016/j.epsc.2022.102289
Received 3 April 2022; Received in revised form 11 April 2022; Accepted 19 April 2022
Available online 4 May 2022

symptoms, acute renal failure and multi-organ system failure [1]. Although it has been reported that the angiotensin-converting enzyme-2 receptor affected by SARS-CoV-2 in the pancreas is expressed more than in the lungs, the issue regarding the occurrence of pancreatitis is controversial. However, it is unknown if SARS-CoV-2 infection causes pancreatic injury and acute pancreatitis or causes an aggravated inflammatory response, and increased risk of organ failure and pancreatic complications leading to increased patient morbidity and mortality [2]. Another mechanism of pancreas damage due to the SARS-CoV-2 infection is indirectly by systemic responses to respiratory failure or the harmful immune response induced by SARS-CoV-2 infection. Acute pancreatitis in children occurs in approximately 1/10.000 children per year. Viral infections are identified as a cause of acute pancreatitis in approximately 8%–10% of cases in children with other common causes being biliary/obstructive (10%–30%), medications (5%–25%), and trauma (10%–20%) [3]. Several viral diseases were reported to be connected with acute pancreatitis, thus making the association between SARS-CoV-2 and pancreatitis plausible [4,5]. We hereby report a case of COVID-19 resulting in acute haemorrhagic necrotizing pancreatitis in 7 years old girl.

2. Case report

A 7-year-old polystigmatized girl with microcephaly and B-negative agammaglobulinemia was admitted to emergency department due to progression of pneumonia. The patient had no abdominal symptoms. Nasal swab for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) tested positive. Physical examination was as follows: blood pressure of 107/67 mmHg, pulse rate of 127 beats per minute, respiratory rate of 30 breaths per minute, temperature of 34.2 °C, and oxygen saturation of 80% on room air, moreover scattered wheezing, she was hemodynamically instable with signs of respiratory distress. The abdomen was soft, nondistended and no tender. Initial laboratory workup summarized in Table 1 demonstrated leucocytosis, an increase in white blood cell count with neutrophila, low lymphocyte level, low albumin and elevated C-reactive protein (Table 1). An arterial blood gas analysis noted metabolic acidosis. Chest CT scans were notable for the presence of multifocal bilateral ground-glass opacities (Fig. 1). High flow cannula oxygenation, bronchodilatation therapy, empiric antibiotic therapy, systemic corticosteroid therapy, thromboprophylaxis and intensive monitoring were placed in use for the patient. Intravenous immunoglobulin was employed on 2nd day of hospitalization. On day 6, due to the Acute Respiratory Distress Syndrome (ARDS), patient required a mechanical ventilation with vasoactive drugs: noradrenaline and complex COVID-19 therapy (antiviral treatment (Favipiravine). We continued in antibiotic and antimycotic treatment. Despite all supportive care, patient's clinical status was declining. On the 16th day of hospitalization she had progressive abdominal distension with decreased bowel sounds. The abdominal ultrasonography (USG) showed paralytic ileus, diffusely increased echogenicity of mesentery and ascites with volume of approximately 120 ml, no abnormality related to the gallbladder, bile ducts and pancreas. There was a progression of ascites and a picture of diffuse intestinal pneumatosis on ultrasound. Bloody stools occurred and we assumed abdominal sepsis, an amount of 100 ml of haemorrhagic fluid was drained. In collaboration with a clinical pharmacologist, we have escalated antibiotic treatment and her inflammatory markers dropped. Nevertheless, her abdominal findings were not improved, dark-blooded waste from the rectum and abdominal drain persisted. Following a 49-day stay in the Paediatric Intensive Care Unit (PICU), due to the clinical and radiological signs of acute abdomen and to the rapid deterioration in the clinical status, an indication to proceed with urgent surgery was made. Pre-operative laboratory parameters are noted in Table 1. After transection of the gastro-colic and duodeno-colic ligament, exposure of necrotic pancreas was made with blunt dissection.

Table 1
Laboratory parameters on admission and before surgical intervention.

Laboratory test	Normal range	On admission	Before surgery
WBC count (10^9 cells/L)	4.5–13.5	15.24	26.94
Neutrophil (%)	45–68	91.9	84.4
Lymphocyte (%)	23–45	6.9	9.5
Procalcitonin (ug/l)	<0.50	0.18	9.6
C-reactive protein (mg/l)	<0.50	126.5	183.5
Haemoglobin (g/dl)	11.5–15.5	10.4	10.3
Platelet count (10^9 cells/L)	150–450	277	81
Haematocrit (%)	35–45	32.6	31.8
AST (ukat/l)	<0.85	1,24	1.04
ALT (ukat/l)	<0.75	0.28	0.21
GMT (ukat/l)	<2.16	0.48	0.95
Albumin (g/l)	35–50	21.3	22.0
Amylase ukat/l	<1.7	–	0.06
Lipase (ukat/l)	0.67–2.34	–	0.29
Blood sodium level (mmmo/l)	130–150	143	138
Blood potassium level (mmo/l)	3.50–5.50	4.6	3.6
Blood calcium level (mmo/l)	1.20–1.35	1.31	1.92
Albumin (g/l)	35–50	21.3	22
Triglyceride (mmol/l)	<1.3	1.15	2.45
pH	7.36–7.44	7.34	7.33
pCO2 (kPa)	4.4–6.0	6.3	8.6
BE (mmol/l)	−3.0–3.0	−1.0	6.4
HCO3 act. (mmol/l)	22–26	24.5	33.3
Sat. 02 (%)	93–98	87.9	80.6

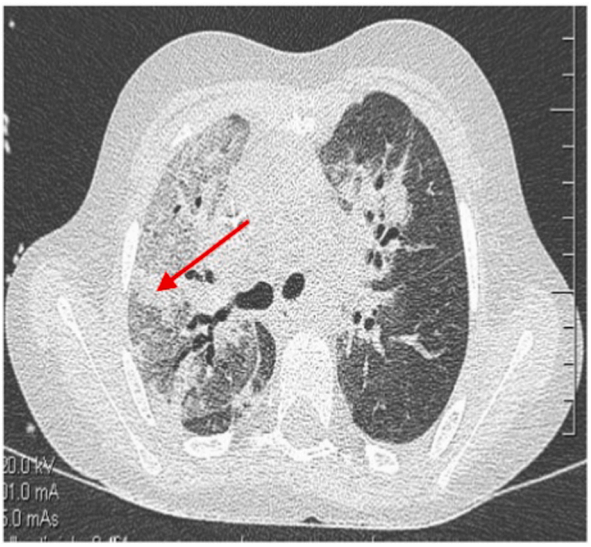

Fig. 1. Chest CT scan: multiple ground glass opacities (GGO) (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Afterwards, a debridement of necrotic tissue (Fig. 2) was performed. Intra-operatively approximately 500 ml of necrotic-haemorrhagic intraabdominal fluid was drained. Continuous lavage and drainage placement were performed. Histology: completely necrotic adipose tissue stained with bile was found along with acinar cell necrosis (Fig. 3). During the post-operative period, patient required aggressive mechanical ventilation and insulin therapy for persistent hyperglycaemia. The CT scans reported necrosis of the pancreas (Fig. 4) and we observed elevation of amylase and lipase in peritoneal lavage sample. The patient received complete intensive supportive care. Unfortunately, despite active intensive therapy, the patient's condition did not improve and she died 38 days after laparotomy as a result of multi-organ failure.

3. Discussion

Symptoms of COVID-19 infection in paediatric patients include both respiratory and gastrointestinal symptoms. Gastrointestinal involvement has been reported in patients with COVID-19 infection with a prevalence of approximately 10% in both adults and children [6,7]. Most common symptoms include diarrhoea, nausea or vomiting and abdominal pain, however recent evidence shows that other organs such as liver or pancreas can also be affected [8]. The mechanism of how COVID-19 infection can cause acute pancreatitis is unclear. It may be related to direct infection of the pancreas by the virus, as has been reported for other viruses, or due to the SARS-CoV-2 receptor of angiotensin-converting enzyme 2 (ACE2) which is highly expressed in pancreas [9]. Acute pancreatitis is

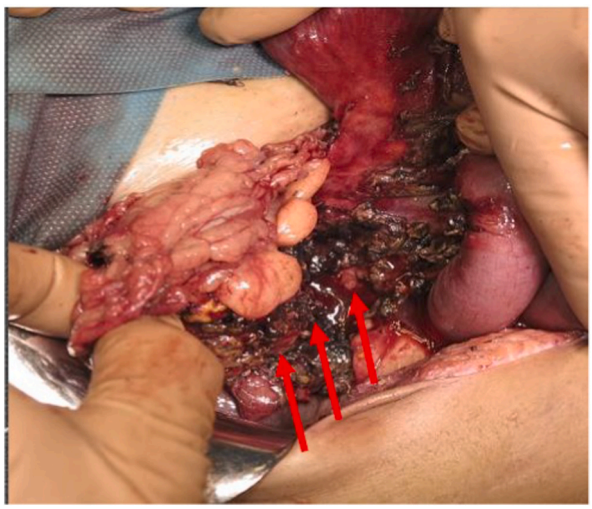

Fig. 2. Intra-operatively: necrotic pancreatic tissue in the lesser sac (red arrows).. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

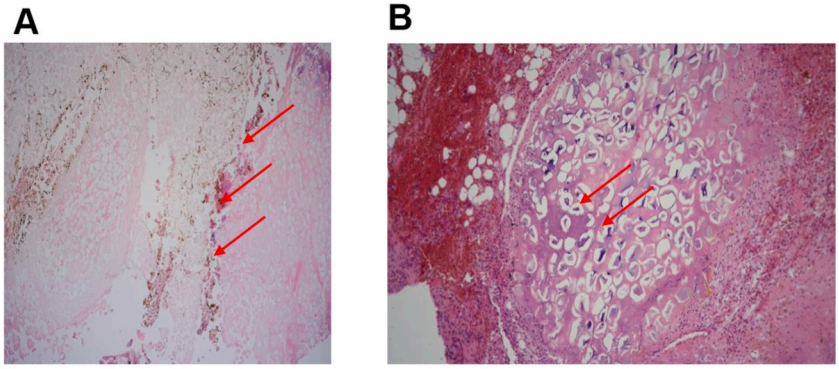

Fig. 3. Histologically: a. completely necrotic adipose tissue stained with bile, b. released fatty acids complex with calcium to form soaps, shown by red arrows. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

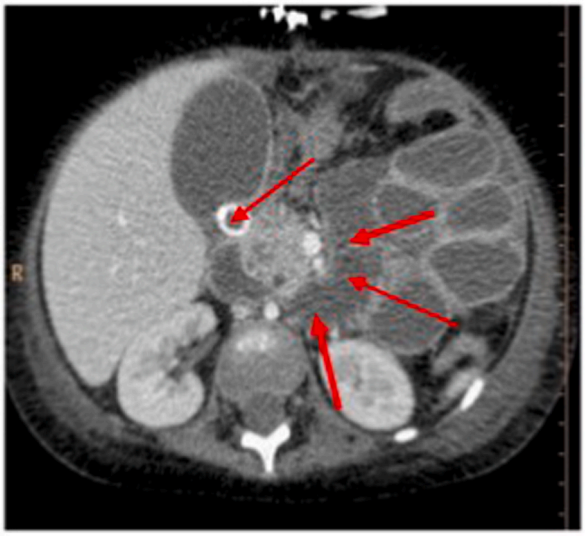

Fig. 4. Abdominal CT scan with contrast: pancreatic head necrosis and spread of inflammation around the pancreas as shown by red arrows. Drainage placed in the gallbladder space. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

diagnosed based on the Atlanta Classification System, whereas at least two of the three following criteria should be found: abdominal pain (defined as acute onset, persistent, severe epigastric pain often radiating to the patients' back), increased serum lipase or amylase levels to greater than 3 times the upper limit of normal value, and characteristic findings of AP on contrast-enhanced CT [10]. In our patient we diagnosed acute necrotizing pancreatitis during the acute surgery, histologically and on the post-operative CT scan. To date, the association between COVID-19 infection and pancreatitis has been limited to a few case reports, mostly in adult patients. Wang et al. were the first who described this connection in a case series of 52 patients, 9 of whom were diagnosed with AP, six patients were found to have abnormal blood glucose levels. They suggested that the pancreatic injury in COVID-19 might be caused directly by the cytopathic effect mediated by local SARS- CoV-2 replication. On the other hand, the pancreatic injury might be caused indirectly by systemic responses to respiratory failure or the harmful immune response induced by SARS-CoV-2 infection, which also led to damage in multiple organs [11]. Bikdeli et al. demonstrated the connection between SARS-CoV-2 infection and thrombotic diseases in several ways. Firstly, direct effects of COVID-19 or the indirect effects of infection, such as via severe illness and hypoxia, may predispose patients to thrombotic events. Additionally, the severe inflammatory response, critical illness, and underlying traditional risk factors may all predispose to thrombotic events, similar to prior virulent zoonotic coronavirus outbreaks. Moreover, the endothelial location of the ACE2 (and transmembrane protease, serine 2 (TMPRSS2) receptors) and response to SARS-CoV-2 infection may cause increased thrombophilia in pancreas vessels in COVID-19 patients, and this vascular thrombosis may lead to AP [12]. Arbati et al. for first time demonstrated case report of patient with necrotizing pancreatitis associated with SARS-CoV-2 infection. A 28-year-old man was referred to the emergency department with diagnosis of acute respiratory distress syndrome. Moreover, the patient also complained of severe stabbing abdominal pain in the epigastric region with radiation to the back with frequent nausea and vomiting. CT scan and laboratory examination proved acute necrotizing pancreatitis, his nasal swab for SARS-CoV-2 reverse transcription-polymerase chain reaction was positive. The patient received supportive care and was discharged after a 15-day hospitalization [13]. Sanchez et al.

demonstrated a case report of 16-years old boy with acute pancreatitis with COVID-19 infection. He was presented with 3 days of nausea, nonbloody, nonbilious emesis, and epigastric pain. Nasal swab for SARS-CoV-2 utilizing RT-PCR methodology was positive. He was diagnosed with acute pancreatitis (epigastric abdominal pain, elevated lipase, and CT scan findings consistent with acute pancreatitis). He received 6 days of treatment and improved [14]. Samies et al. presented a case series of 3 paediatric patients who were diagnosed with pancreatitis about a week after the onset of COVID-19 symptoms. All 3 patient were treated conservatively and were discharged in good medical conditions. Authors suggest that the association between SARS-CoV-2 and acute pancreatitis is possible as in another several viral diseases, including mumps, measles, Epstein-Barr virus, hepatitis A and E, and Coxsackievirus [15]. Necrotizing pancreatitis is rare in children. According to the literature, necrotizing pancreatitis occurs in less than 1% of children with acute pancreatitis. Among the five large sample paediatric cases reported in the United States, only 3 of 1014 children with acute pancreatitis had pancreatic necrosis, which was significantly less severe than that of adults [16]. Mortality rate in acute pancreatitis is low, overall lower than 5% [17].

4. Conclusion

COVID-19 is an aggressive pulmonary infection that could lead to the respiratory distress syndrome and multi-organ dysfunction. Acute pancreatitis should be suspected in patients infected with COVID-19 who have risk factors for pancreas damage.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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