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Coronavirus Disease and Abdominal Pain: Mechanism, Diagnostic, and Treatment

Aleksandra Bozhinovska*

Department of Surgery, City General Hospital 8 September, Skopje, Republic of Macedonia

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***Correspondence:** Aleksandra Bozhinovska, City General Hospital 8 September, Skopje, Republic of Macedonia. E-mail: abozhinovska@yahoo.com
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Abstract

BACKGROUND: On March 11, 2020, the General Director of the World Health Organization has announced that according to the organization, the level of spread and severity of symptoms of coronavirus disease (COVID-19) is becoming alarming and because of that, it can be characterized as a pandemic. The assessment of the World Health Organization stimulated more urgent and belligerent actions from the governments as the number of case reports and studies on COVID-19 symptoms and treatment increased dramatically.

AIM: In this paper, the aim is to make a review of the studies and case reports/series that indicate that abdominal pain is one of the manifestations of COVID-19.

METHODS: A search was performed on two electronic databases: PubMed Central and Google Scholar, using the key words "COVID-19 and abdominal pain." Case reports and case series in adults and children were included regardless of the language, region, or the publication date. The methods of synthesis and comparison were also used.

RESULTS: In general, it can be noted that the manifestation of the COVID-19 infection on the digestive tract and the consequences on the same are not fully examined.

CONCLUSION: The conclusion of the analyzed papers is that clinical practitioners in COVID-19 pandemic should carefully distinguish abdominal pain and other GI symptoms from COVID-19 manifestations and should exclude acute surgical condition.

Introduction

Severe and acute abdominal pain is almost always a symptom for intra-abdominal disease that requires a surgical treatment (condition termed as acute abdomen). From a pathophysiological perspective, abdominal pain is divided as visceral, somatic, and referred pain.

Recent studies indicate that coronavirus disease (COVID-19) can also be a possible cause of abdominal pain. According to Widyadharma *et al*. [1], the mechanism of pain in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive patients "is associated with two-way communication between the gut microbiota and the brain, namely, between the endocrine (cortisol), the immune system (cytokines), and nerves (vagus nerve and enteric nervous system)." Namely, ACE2 receptors which are the target of SARS-CoV-2, in humans, are found on the luminal surface of the redifferentiated small intestinal epithelial cells and in crypt and colon cells [1], [2]. It is implied that the described mechanism is the reason for presentation of abdominal pain without respiratory symptoms in some, atypical, SARS-CoV-2-positive patients.

In this era of SARS-CoV-2 pandemic, it is important to rule out the acute surgical condition which needs emergency operation, having in mind that SARS-CoV-2 infection may be presented with abdominal pain and other GI symptoms. To do so, for clinical practitioners, it is important to have sufficient information about the scope of gastrointestinal (GI) symptoms manifested in COVID-19-positive patients. Therefore, in the following parts of the paper, the available case reports regarding this topic are presented.

Abdominal Pain in Adults with COVID-19

At the beginning of the COVID-19 pandemic, the clinical features of the novel coronavirus were mainly described as respiratory. However, as the time passed, the understanding of the COVID-19 evolved and it was concluded that COVID-19 can cause multiple organ dysfunction. Namely, the variety of the symptoms of the novel COVID-19 has rapidly increased. According to Liu *et al*. [3], the typical initial symptoms of COVID-19 include fever, cough, and muscle pain or fatigue, while the less typical symptoms of the infection reported are heart palpitations, diarrhea, and headache.

Besides the manifestations on the respiratory system, the smell and taste disorders (anosmia and dysgeusia, respectively), GI symptoms of COVID-19, and abdominal pain are also reported as less typical symptoms. The chronic respiratory disease report as of

May 30, 2020, in the USA, among 373,883 confirmed COVID-19 cases with data on individual symptoms, 28,443 have reported abdominal pain, which is 7.6% [4]. In addition, in this report, it is noted that nausea/vomiting was reported in 42,813 cases (or 11.5%), while diarrhea was present in 72,039 cases (or 19.3%) [4].

However, various authors suggest that GI symptoms may be underestimated and indicate that abdominal pain, diarrhea, nausea, vomiting, and lack of appetite, in some cases are presented before [5] or together with mild respiratory symptoms. Zang *et al*. [6] suggested that patients with GI symptoms had longer duration between symptom onset and viral clearance.

In the following table (Table 1), the reported cases of SARS-CoV-2-positive patients with abdominal pain are summarized. It is important to note that some of them had also other GI symptoms, while others were without other GI symptoms. In addition, in regard to the localization of the abdominal pain, it can be concluded that most of the patients in the presented case reports experienced epigastric pain or diffused abdominal pain. Furthermore, significant number of patients has described pain in the right iliac fossa.

To sum up, although at the early stages of the pandemic, the papers focused on the clinical characteristics of COVID-19, classified the GI symptoms as uncommon [7], the authors of the presented case reports have shown that manifestation of the disease on the digestive tract can be challenging for diagnostics. Besides, it is noted that in these cases, a computed tomography (CT) on the abdomen is the most commonly used diagnostic technique, while the ultrasound scan can also give good information regarding diagnostics. However, on the abdominal CT, in most of the cases, the lower parts of the lungs

Table 1: Summary of the case reports analyzed in adults

S. No.	Case/author	Abdominal pain region	Other GI symptoms	Fever	CT abdomen	CT chest (at presentation), (or chest X-ray done instead)
1	Widyadharma *et al*. [1]	Persistent stabbing pain that originates in the groin and migrates to the abdomen, pelvis, back, and chest	None	Yes	Pulmonary ground-glass opacification, pneumonia type of consolidation, potential sigmoid colitis, and distal descending colon	NA
2	Saeed *et al*. [2]	Epigastric	Nausea, vomiting	No	Normal	Bilateral ground-glass opacities
3	Saeed *et al*. [2]	Epigastric	Nausea, vomiting	Yes	Normal	Bilateral ground-glass opacities
4	Saeed *et al*. [2]	Global	Nausea	Yes	Normal	Bilateral ground-glass opacities
5	Saeed *et al*. [2]	Left iliac fossa	Nausea, vomiting	Yes	Normal	Bilateral ground-glass opacities
6	Saeed *et al*. [2]	Right iliac fossa	Nausea	Yes	Normal	Bilateral ground-glass opacities
7	Saeed *et al*. [2]	Global	Nausea, vomiting	No	Normal	Bilateral ground-glass opacities
8	Saeed *et al*. [2]	Right iliac fossa	Nausea, vomiting	No	Cholecystitis	Normal
9	Saeed *et al*. [2]	Right iliac fossa	Diarrhea	Yes	Appendicitis	Normal
10	Saeed *et al*. [2]	Umbilical	Nausea	No	Ileus	Normal
11	Walpole *et al*. [14]	Severe abdominal pain (renal colic susp.)	Vomiting, diarrhea	Yes	Normal	Multifocal peripheral patches of consolidation – >3 cm in diameter with air bronchograms running through – in all but the left upper lobe
12	Ahmed *et al*. [15]	At first diffused, later localized to the right lower quadrant	Diarrhea, vomiting	Yes	Diffuse paracolic gutters fat stranding, mild free fluid, bilateral mild pleural effusion with consolidations, and filling defect at superior mesentery vein that is attributed to streaming artifact or thrombosis	Initial chest X-ray** normal; repeated chest X-ray** showed bilateral infiltrates
13	Ahmed *et al*. [16]	Right iliac fossa	Nausea, vomiting	Yes	Normal	Upper cut bilateral basal lung consolidation
14	Ahmed *et al*.[16]	Right upper quadrant	None	No	Right hypochondria epiploic	Normal
15	Ahmed *et al*. [16]	Epigastric	Nausea, vomiting	Yes	Normal	NA
16	Abdalhadi *et al*. [17]	Right iliac fossa	Nausea, vomiting	No	Normal	Bilateral patchy peripheral lung basal consolidation and ground-glass attenuations
17	Pazgan-Simon *et al*. [18]	Global	None	No	Normal	Interstitial consolidations in the lower lobes of both lung bases
18	Voutsinas *et al*. [19]	Right lower quadrant	None	No	Normal	Hazy ground-glass opacities in the dependent portions of both lung bases
19	Voutsinas *et al*. [19]	Flank pain	Nausea, vomiting	Yes	Normal	Peripheral ground-glass opacities with associated increased interstitial markings in both lung bases
20	Voutsinas *et al*. [19]	Abdominal pain	Diarrhea, blood stool	No	Mild sigmoid colitis	Ground-glass opacification with a rounded morphology in the periphery of the right lung base
21	Voutsinas *et al*. [19]	Epigastric and flank pain	Nausea	No	Pyelonephritis	Rounded ground-glass opacities in the periphery of the imaged right lower lobe
22	Mahan *et al*. [20]	Periumbilical pain	None	No	None	Abdominal aorta showed thromboemboli, diffuse bilateral ground-glass opacities in the lungs
23	Gérald *et al*. [21]	Epigastric pain and RUQ sensitivity	Nausea	No	Bilateral subpleural irregular lines and scattered peribronchial ground-glass opacities at both lung bases	NA
24	Gérald *et al*. [21]	Epigastric pain	None	Yes	No abdominal abnormal finding but demonstrated bilateral subpleural ground-glass opacities with intralobular reticulations at the lung bases	NA
25	Gérald *et al*. [21]	Diffuse abdominal pain without guarding	Nausea and diarrhea	No	Demonstrating predominantly right lower lobe crazy-paving associating ground-glass opacities and interlobular reticulations	NA
26	Purayil *et al*. [22]	Epigastric pain	Vomiting	Yes	Ultrasound scan* of the abdomen was normal	Chest X-ray** revealed bilateral infiltrates
27	Altermanini *et al*. [23]	Epigastric pain	None	No	None	Normal

*It was described by an ultrasound scan on the abdomen, **it was done by chest X-ray, not CT on the chest. CT: Computed tomography.

or the lungs bases are visible, which is important for detecting any abnormalities in these organs, too.

According to Ye *et al*. [8], the mechanisms that cause GI symptoms in COVID-19-positive patients can be different:

1. Direct infection of GI cells – the expression and distribution of ACE2 in humans is a potential infection pathway for SARS-CoV-2. ACE2 is widely found in human small intestinal epithelial cells, especially in type II epithelial cells. In addition, high expression of ACE2 has been detected in the intestinal epithelial cells, the esophagus, and the lungs. Ye *et al*. suggested that the presence of GI symptoms in COVID-19 patients indicates that SARS-CoV-2 may invade target organs of the digestive tract through ACE2 receptors and cause primary damage. In addition, several authors indicate that SARS-CoV-2 is 10–20 times more transmissible than SARS-CoV. Furthermore, Ye *et al*. hypothesized that ACE2 expressing cells in humans, secretes large number of cytokines which induces cytokines' storm that can cause damage to multiple organs and may also cause immune cell death;
2. GI damage caused by lung infection – which mainly refers to the effect called "gut-lung axis" which means that disorders of the GI flora affect the respiratory tract and vice versa, respiratory tract changes impact the digestive tract through immune regulation;
3. GI symptoms caused by drug's side effects – use of large amount of antibiotics (especially macrolides, cephalosporins, and β-lactam antibiotics), is the most common cause for diarrhea as a side effect in COVID-19-positive patients.

Furthermore, Perisetti *et al*. [9] suggested a classification of four pathogenic mechanisms that cause GI manifestations in COVID-19 patients:

1. Cytopathic effects – SARS-CoV-2 binds on ACE 2 receptors and enters the stomach and small intestine;
2. Gut inflammation – induced pro-inflammatory pathways with increased cytokine release and fecal calprotectin;
3. Altered gut microbiota – increased mTor activity, hypochlorhydria, altered gut-lungs axis;
4. Others – include drug-induced changes, pre-existing condition worsening, and secondary infection.

In general, "after the entry into GI tract, SARS-CoV-2 can exert its cytopathic/inflammatory changes, which can potentially lead to visceral pain. If this is a somatic due to the involvement of the peritoneum or a referred pain is unknown" [9]. However, the exact mechanism of appearance of abdominal pain in COVID-19-positive patients is unclear.

Several case reports also indicate a correlation between COVID-19 and cholecystitis. Authors have presented case of COVID-19 that was associated with acalculous cholecystitis [10], [11], [12]. All patients in reported cases with this condition are aged over 60 years. This condition may lead to gallbladder ischemia, necrosis, and perforation that require emergency surgical operation. They suggested that pathophysiological mechanism is that SARS-CoV-2 binds to ACE-2 receptor in the liver, gallbladder, and bile ducts [13]. Systemic endotheliitis, hypercoagulability, antiphospholipid antibodies, and thrombotic microangiopathy are the other contributors to the occurrence of cholecystitis in COVID-19-positive patients. Furthermore, some reports describe patients with SARS-CoV-2 acute calculus cholecystitis [13] that has had no clinical manifestation of gallstones before this viral infection. The abdominal pain caused by cholecystitis is usually not the first manifestation of SARS-CoV-2 infection (for acalculous cholecystitis).

Abdominal Pain and COVID-19 in Children

Before the COVID-19 pandemic, few studies have focused on the correlation between viral infections (cytomegalovirus, Epstein–Barr virus, hepatitis A virus, and human herpes virus) and acalculous cholecystitis in children [24], [25], [26], [27]. According to these studies, diagnosis of acute cholecystitis may be challenging. Supposed pathogenic mechanism in these cases is direct invasion or inflammation triggered by bile stasis [26].

The literature also provides papers and case reports that depict patients that had COVID-19 manifested with pediatric abdominal pain. These cases can be challenging for diagnostics, in the same way as with adults. The available cases are presented in Table 2.

In the analyzed case reports, it is outlined that in COVID-19 pediatric patients with GI symptoms, adequate imaging studies (ultrasound and CT) should be done to exclude the acute abdomen. The GI symptoms, including abdominal pain, may be only a presentation of the SARS-CoV-2 infection without the need for emergency surgical treatment. Furthermore, some studies prove that the surgical treatment in these patients may deteriorate the condition.

Treatment

The key point in treatment of COVID-19 patients with abdominal pain is to exclude acute surgical suffering. Besides physical examination, adequate imaging studies are necessary.

In adults, the reported cases show that abdominal pain may manifest before respiratory signs

Table 2: Summary of the case reports analyzed in children

S. No.	Case/author	Age and gender	Medical history	Abdominal pain	Other GI symptoms	Fever	CT abdomen	CT chest	SARS-CoV-2 PCR
1	Harwood *et al*. [28]	14 years, Female	No underlying medical conditions	Central abdominal pain which migrated to the right iliac fossa	None	Yes	Abdominal ultrasound scan demonstrated mesenteric adenitis without free fluid and chest X-ray was unremarkable	12 h later, urgent computed tomography scan of the chest and abdomen revealed diffuse intra- and interlobar thickening consistent with SARS-CoV-2 infection and no intra-abdominal pathology	Negative
2	Harwood *et al*. [28]	3 years, Male	Nil	Abdominal pain	Diarrhea and vomiting	Yes	Revealed perforated appendicitis with intra-abdominal collections	NA	Positive
3	Tullie *et al*. [29]	4 years, Male	Autism spectrum disorder	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Mesenteric lymphadenopathy, terminal ileitis, normal appendix	NA	Positive
4	Tullie *et al*. [29]	5 years, Male	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Mesenteric lymphadenopathy and free fluid in right iliac fossa, no bowel wall thickening, normal appendix	NA	Negative
5	Tullie *et al*. [29]	8 years, Male	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Echogenic fat and mild terminal ileal thickening, appendix not visualized, no significant lymphadenopathy	NA	Positive*
6	Tullie *et al*. [29]	11 years, Female	Mild asthma	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Bowel wall thickening involving ileocecal junction with mesenteric lymphadenopathy. Appendix not seen CT abdomen: Fluid-filled appendix with appendicolith but no inflammation. Thickened cecum and multiple enlarged mesenteric lymph nodes	NA	Positive
7	Tullie *et al*. [29]	12 years, Female	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Multiple enlarged lymph nodes in right lower quadrant. Appendix not seen CT abdomen: Non-inflamed retrocecal appendix, terminal ileal thickening and mesenteric lymphadenopathy	NA	Positive
8	Tullie *et al*. [29]	14 years, Male	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Inflammatory changes in ileocecal region associated with lymphadenopathy. No features of appendicitis. (Nb. This was performed after the CT to confirm findings) CT abdomen (non-contrast): Inflammatory change in the right iliac fossa with matted bowel loops. Focal collection and enlarged mesenteric lymph nodes. Collapsed bowel loops, no visible collection or evidence of appendicitis	NA	Positive
9	Tullie *et al*. [29]	15 years, Male	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Inflammatory change and echogenic fat in right iliac fossa, mesenteric lymphadenopathy. Appendix not visualized. CT abdomen: Calcified appendicolith in non-inflamed appendix. Thickening of terminal ileum consistent with terminal ileitis	NA	Negative
10	Tullie *et al*. [29]	16 years, Female	Nil	Abdominal pain	Diarrhea and vomiting	Yes	US abdomen: Terminal ileal inflammation with local lymphadenopathy, normal appendix	NA	Negative
11	Saleh *et al*. [30]	4 months, Male	Ontogenesis imperfecta	Abdominal tenderness	Poor feeding, bilious vomiting	Yes	Coffee bean sign in the left upper quadrant viewed on abdominal X-ray	Typical lesions for SARS-CoV-2 on chest	Positive
12	Saleh *et al*. [30]	10 years, Male	Nil	Abdominal pain, tenderness, and guarding	No	No	US: Signs of appendicitis	Highly suggestive for COVID-19	Positive
13	Saleh *et al*. [30]	5 years, Female	Nil	Abdominal pain, tenderness, and guarding	Vomiting	Yes	US: Signs of appendicitis	Typical lesions for SARS-CoV-2 on chest	NA –contact with SARS-CoV-2-positive patients
14	Saleh *et al*. [30]	45 days, Male	Cerebral palsy, seizures	Abdominal distention and irritability	Oral intolerance	No	Abdominal X-ray: Coffee bean sign	Typical lesions for SARS-CoV-2 on chest	Positive

*Initially SARS-CoV-2 PCR negative, subsequent positive PCR. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, CT: Computed tomography.

of SARS-CoV-2 infection, and therefore, adequate imaging studies are required. It can be noted that in these cases, abdominal CT is the most commonly used diagnostic technique, while the ultrasound scan can also give good information regarding the diagnosis. However, on the abdominal CT, in most of the cases, the lower parts of the lungs or the lungs bases are visible, which is important for detecting any abnormalities in these organs, also. This is the advantage when using abdominal CT scan as a diagnostic tool.

In addition, in adults when acute abdomen is excluded, treatment is based on analgesia, and in some of the presented cases, opioid analgesics were needed for relieving pain. The additional treatment is based on the COVID-19 Protocols and Guidelines. Furthermore, the use of probiotics may improve GI symptoms in patients diagnosed with COVID-19. According to Falch *et al*. [31], most appropriate treatment of abdominal pain when the need for surgery is ruled out includes opioid or non-opioid analgesics. Opioid analgesics bind to opioid receptors both in the central nervous system and in peripheral tissues to provide pain relief. Non-opioid analgesic agents are divided into acidic which mainly accumulate in tissues with a low pH (such as tissue with active inflammatory processes, the kidneys, and the stomach) and non-acid anti-pyretic analgesics which distribute to all tissues. The intensity of pain is crucial for determining the type of analgesics that need to be used. The administration of the drugs largely depends on the estimated potential for enteric absorption of the delivered agent [31].

Mattone *et al*. suggested that in the cases of COVID-19-positive patients that developed acute cholecystitis, although laparoscopic cholecystectomy is considered the gold standard, Tokyo Guidelines advice to delay surgical operation and to perform the percutaneous gallbladder drainage for surgically high-risk patients with acute cholecystitis and comorbidities.

As presented in the case reports in the previous section, in children, the abdominal pain and other GI signs are usually presented later, during hospital stay of the patients, and often mimicking atypical appendicitis or volvulus. Therefore, in the case reports described above, when explorative laparotomy or laparoscopy was executed, the intraoperative finding was peritoneal lymphadenopathy and/or serous peritoneal effusion. According to Hijaz *et al*., "…pediatric patients in general are at risk for receiving less than optimal analgesia. In the setting of acute AP (author remark: Abdominal pain), providers are often concerned about the possibility that strong analgesia (e.g., opioids) may mask symptoms and result in complications and increased morbidity. Several prospective, randomized studies have shown that judicious use of analgesia may enhance diagnostic accuracy by permitting a more thorough physical examination. It appears that opioids may be used to treat acute AP in children without delaying the diagnosis" [32].

Conclusion

According to the literature review, abdominal pain may be the first sign of SARS-CoV-2 infection in adults, occasionally without any respiratory symptoms and fever. In the further development of the disease, the abdominal pain relievers and the other respiratory symptoms prevail. Acute acalculous cholecystitis may be present in SARS-CoV-2-positive patient with severe clinical manifestations.

In the described case reports of children, the situation is different. Namely, in the analyzed cases, the abdominal pain and GI symptoms worsened after the patients were diagnosed with SARS-CoV-2 infection and were hospitalized due to the severity of other symptoms.

Overriding conclusion of the analyzed papers is that clinical practitioners in COVID-19 pandemic should carefully distinguish abdominal pain and other GI symptoms from COVID-19 manifestations and should exclude acute surgical condition.

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