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Duodenal Endoscopic and Histopathologic Findings in a COVID-19 Patient: A Case Report and Literature Review

Vahatra Joëlle Razafimahefa[1], Jocia Fenomanana[2], Manoahasina Ranaliarinosy Rabarison[3], Soloniaina Hélio Razafimahefa[4], Tsitohery Francine Andriamampionona[1]

[1]Department of Pathology, CHU Andrainjato, Fianarantsoa, Madagascar
[2]Department of Biology, CHU Andrainjato, Fianarantsoa, Madagascar
[3]Department of Pathology, CHU Joseph Ravoahangy Andrianavalona, Antananarivo, Madagascar
[4]Department of Internal Medicine and Gastroenterology, CHU Andrainjato, Fianarantsoa, Madagascar
Email: rootsrazaf@yahoo.fr

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Abstract

Although COVID-19 clinical manifestations are mostly respiratory gastrointestinal manifestations may also be encountered in some instances. However, at the time of our writing, little is known about COVID-19, associated pathologic changes in the digestive system. We describe a case of COVID-19 disease with digestive manifestations that demonstrated specific pathologic changes in the gastrointestinal tract. Histological examination of endoscopic biopsy samples from duodenum was performed in combination with a review of the literature. According to our literature review, digestive histopathologic changes have been reported in 14 cases of COVID-19 patients. Pathological findings were generally nonspecific in all these cases and ranged from epithelial damage, lymphoplasmacytic and macrophages infiltrates, prominent endothelitis and ischemic enterocolitis. In our patient, histological features were more specific, characterized by several viral cytopathic effects associated with mucosal damage, numerous microthrombi and positive staining of ACE2 on various enterocytes. Histological analysis is not a practical option for the diagnosis of SARS-CoV-2 infections but could help to elucidate pathophysiology of the disease. Those changes may be specific in the GI tract and related clinical manifestations should not be overlooked. Furthermore, preventive measures for oral-fecal transmission should not be minimized.

Keywords

COVID-19, SARS-CoV-2, Histopathologic Findings, Duodenum, Endoscopy, Biopsy

1. Introduction

Coronavirus Disease-2019 (COVID-19) is an infectious viral disease since it erupted in Wuhan, China in late 2019 [1]. The disease spread rapidly and was declared an official pandemic by the World Health Organization (WHO) on March 11, 2020. By the end of July, 2020, there were more than 15 million confirmed cases and over 640,000 deaths reported worldwide [2]. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) cell receptor to invade human cells. This host-cell receptor can be found in various organs, suggesting that SARS-CoV-2 may infect other tissues aside from the lungs which could result in variable symptoms [3]. Most patients with COVID-19 present with typical respiratory symptoms with fever while others have gastrointestinal (GI) manifestations such as diarrhea, vomiting and abdominal pain [4]. Despite the rising number of studies on histopathologic findings of COVID-19 in various organs, less is known about GI pathologic changes related to this viral infection. Herein we report a case of COVID-19, diagnosed by duodenal endoscopic biopsy, confirmed by immunohistochemistry and GeneXpert COVID-19 RNA polymerase chain reaction test. The present manuscript is aimed to provide the relevant morphologic findings observed in duodenum resulting from SARS-CoV-2 infection in order to understand its pathophysiology and to improve our treatment strategy. To our knowledge, this is one of the first reports in the English literature that described specific pathologic changes associated with COVID-19 in the digestive system.

2. Observation

A 62-year old man without significant past medical history and no clear contact history with COVID-19 presented to our hospital with nausea and stabbing epigastric pain radiating to the back for two weeks. On presentation, he was afebrile with normal heart rate, blood pressure and oxygen saturation. His physical examination revealed no specific findings. On hospital day 2, he began to develop low-grade fever, vomiting and mild diarrhea associated with severe epigastric pain. Laboratory evaluation was notable for an elevated serum lipase exceeding twice the upper limit of normal. The laboratory testing results and corresponding analyses are summarized in **Table 1**. Abdominal computed tomography (CT) imaging was normal (**Figure 1**). Electrocardiogram was performed and revealed sinus rhythm without evidence of ischemia. Given his persistent epigastric pain and worsening diarrhea, an upper GI endoscopy was performed, which revealed a grossly rugged duodenum, which was subsequently biopsied. The remaining portions of the GI tract were normal. Histological examination revealed preserved villus height with epithelial dystrophy and denudation (**Figure 2**). The lamina propria showed marked inflammation with lymphoplasmacytic and eosinophilic infiltrates that caused focal glandular damage. Residual glands demonstrated viral cytopathic effects such as enlarged cells with vacuolated cytoplasm, large smudged nuclei, and intranuclear inclusions. Numerous

Table 1. Laboratory evaluation of the current case.

Variable	Results	Normal range
Alanine aminotransferase (U/liter)		<40
Aspartate aminotransferase (U/liter)	15	<40
Lipase (U/liter)	**148**	**<60**
Fasting plasma glucose (mmol/liter)	6.37	4.20 - 6.40
Creatinine (μmol/liter)	78	44 - 115

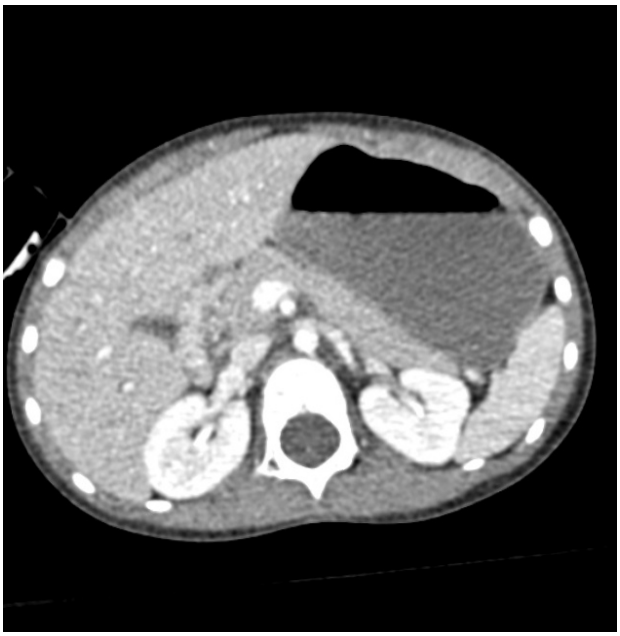

Figure 1. Abdominal computed tomography. No evidence of pancreatic injury.

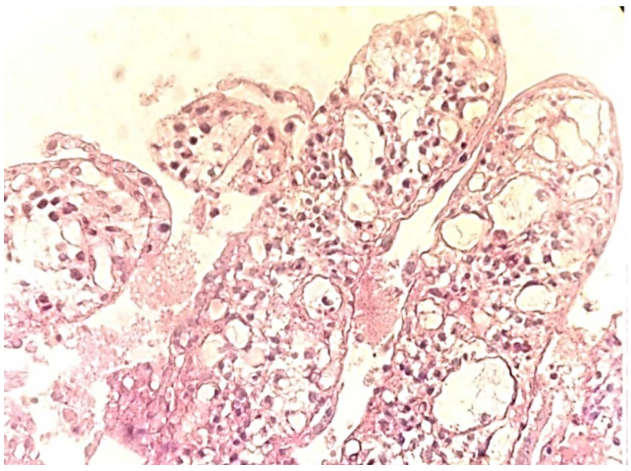

Figure 2. Duodenal mucosa: Preserved villus height with glandular and surface epithelium denudation. Enlarged residual epithelial cells are also seen. The lamina propria showed a mixed inflammatory infiltrate with some eosinophilic polynuclear cells (Hematoxylin and Eosin Stain ×400).

microthrombi were also found as well as positive staining of ACE2 on various enterocytes. Based on these findings, the unusual clinical course and the current context of the COVID-19 pandemic, his nasal swab was tested for SARS-CoV-2 using GeneXpert and was positive. The patient received azithromycin, anticoagulation, analgesics and antidiarrheals. On hospital day 17, his overall clinical condition improved. He was discharged at day 22. After 3 months, follow-up serology was negative for COVID-19. The patient was alive and well and had no complaints.

3. Discussion

COVID-19 constitutes the world's most pressing public health threat and has a significant impact on people's lives around the world. The clinical presentation ranges from asymptomatic to severe respiratory illness [5]. Over the course of this current pandemic, it has become apparent that some patients can present with GI symptoms with a paucity of other manifestations, possibly leading to misdiagnosis and potentially serious consequences for them and their contacts [4] [5]. Here we report a case of a 62-year old man with COVID-19, whose principal symptoms were epigastric pain with nausea, vomiting and diarrhea. As the laboratory evaluation revealed an elevated serum lipase, acute pancreatitis was initially suspected but was secondarily eliminated given the normal pancreas appearance on abdominal CT imaging. This suggests that the elevated serum lipase reflected GI manifestations of SARS-CoV-2 infections, including gastritis, enteritis and colitis, rather than pancreatic injury [6].

Existing literature has demonstrated the presence of ACE2 receptors within the GI epithelial cells that act as entry receptors for the COVID-19 virus. This viral receptor is found in both the upper and lower GI tract where it is expressed at nearly 100-fold higher levels than in respiratory organs [3]. This might be the plausible explanation of GI manifestations due to direct virus attack on the digestive system or tissue damage secondary to an immune response [7]. Several studies have described this GI tropism of SARS-CoV-2 that could be confirmed by viral detection in stool samples [7] [8]. In our case, the context of COVID-19 was initially overlooked, and the persistence of epigastric pain with worsening diarrhea resulted in endoscopy being performed. In the literature, one case of endoscopy [9] [10] and two cases of colonoscopy [11] have been performed in COVID-19 patients with acute GI bleeding. Esophageal mucosal lesions were observed in the first case, without endoscopic abnormalities in the rest of the GI tract. The mechanisms of that esophageal damage were still not fully understood. In the other two cases, colonoscopies were characterized by scattered erosions and ulceration within the cecum and the ileocecal valve that were clinically consistent with ischemia [9] [10] [11]. In the present case, endoscopic findings were unusual and consist of a rugged appearance of the duodenum and normal mucosa in the rest of digestive tract. Histological examination demonstrated mucosal damage with epithelial dystrophy and denudation associated with marked

inflammation within the lamina propria that also caused glandular damage. Viral cytopathic effects were also seen in residual glands. These were characterized by enlarged cells with vacuolated or ballonised cytoplasm, large smudged nuclei and intranuclear inclusions. Additionally, numerous microthrombi were noticed and positive staining of ACE2 was also found on various enterocytes. To our knowledge, this is the first report in the English literature providing specific details of the pathologic changes associated with COVID-19 in the digestive system since the outbreak of this viral pandemic. Only non-specific histopathological changes (e.g. epithelial damage, villus blunting, and chronic inflammation) are found in most known viral infections of the small intestine. However, GI cytopathic effects associated with COVID-19 should be differentiated on histology from those of GI cytomegalovirus (CMV) disease [12] [13]. The latter are usually found in endothelial and mesenchymal cells that are cytomegalic and two to fourfold larger than normal and contain basophilic intranuclear inclusions surrounded by a clear halo, giving the appearance of an owl's eye that stain positively with CMV antibody [12]. As described in the present case, cytopathic viral effects have been seen in both endothelial mesenchymal and glandular cells in COVID-19 enteritis and were associated with the predominance of microthrombi. Besides, positive immunohistochemical staining for ACE2 protein confirmed the diagnosis. Since the emergence of the COVID-19 pandemic, associated GI histopathologic changes of this viral infection have been reported in 14 cases, nine in postmortem sampling of deceased patients [11] [14] [15], one from small intestine specimens in the context of mesenteric ischemia [11], one of rectal resection in a patient with rectal adenocarcinoma [16], and in three cases, endoscopic [9] [10] and colonoscopic biopsies [13] in the context of GI bleeding. General characteristics of these cases are summarized in **Table 2** and **Table 3**. Pathological findings were generally nonspecific in these cases and ranged from epithelial damage, lymphoplasmacytic and macrophages infiltrates, prominent endothelitis and ischemic enterocolitis. In addition, immunofluorescence showed that viral receptor ACE2 and viral nucleocapside NP were abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelia; in lymphocytes and macrophages in the lamina propria and also in endothelial cells but rarely in the esophageal mucosa [9] [10] [13]. These reported differences for ACE2 and NP expressions could also explain the variable distributions and predominance of mucosal lesions along the GI tract. Moreover, SARS-CoV-2 virions have been observed in rectal tissue, under electron microscopy in one patient and SARS-CoV-2 nucleic acid has been detected in the same rectal specimen using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) [16]. In our patient, diagnosis of COVID 19 was confirmed by detection of SARS-CoV-2 nucleic acid from nasal swab, using GeneXpert.

We noticed that the patient took longer to report for medical care, a tendency that has already been reported in the literature in an important subgroup of

Table 2. Summary of COVID-19 cases with GI histopathology findings in postmortem sampling.

Case	Reference	Patient Age (y)	Patient Sex	Clinical characteristics	GI pathology findings	Additional investigations	Treatment	Cause of death
1	11	**71**	**M**	- Male renal transplant recipient with coronary artery disease and hypertension. - Deteriorated condition following COVID-19 diagnosis.	Dominant mononuclear cell infiltrates within the intima along the lumen of many vessels in the small intestine.	NOS	MV	Patient died on HD8 from multisystem organ failure.
2	11	**58**	**F**	- Hypertension, diabetes and obesity. - Respiratory failure, followed by multiorgan failure. - HD16: mesenteric ischemia, removal of necrotic small intestine.	Endothelitis of the small intestine submucosal vessels.	NOS	NA	- ST—segment elevation myocardial infarction, right heart failure and circulatory failure, cardiac arrest.
3	14	63	M	- No clear exposure history with COVID-19. - Presence of comorbidities in cases 3 and 4 with respectively diabetes and both lung bronchiectasis; a history of oral cancer and hyperglycemia. - COVID-19 diagnosis through throat swab tests and chest CT. - D5 of illness: cough, runny nose, low-grade fever, fatigue, dyspnea, palpitations, discomfort. - D10: severe pneumonia. - Total course of illness from onset to death: 17 - 19 days.	- Partial epithelial degeneration. - Necrosis and shedding of gastric and intestinal mucosa. - Expansion and hyperemia of small blood vessels in the lamina propria and submucosa; lymphocytes, monocytes and plasma cells infiltration.	Gastric and intestinal tissues tested negative for SARS-CoV-2 nucleic acid.	Recombinant human interferon α1b, Kelizhi, thymopentin, methylprednisolone sodium succinate, human immunoglobulin.	NOS
4	14	69	M					
5	14	79	F					
6	15	52	M	Obese patient tested positive for COVID-19.	Ischemic enterocolitis.	NOS	CPR	Sudden cardiac death.

Continued

7	15	71	M	Hypertension with nicotine abuses and granulomatous pneumopathy.	Ischemic enterocolitis.	NOS	CA, MV	Respiratory failure pneumonia.
8	15	63	M	Patient with T2DM, obesity and bronchial asthma.	Ischemic colitis.	NOS	CA, MV, lysis of right ventricular thrombus, CPR.	Cardiorespiratory failure, PE.
9	15	87	F	Patient with non-small cell lung cancer, COPD, CHD and CKD.	Pseudomembranous colitis.	NOS	BSC	Respiratory failure, viral pneumonia.

BSC: best supportive care; CA: catecholamine therapy; CHD: chronic heart disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CPR: cardiopulmonary resuscitation; D: day; HD: hospital day; MV: mechanical ventilation; NA: not available; NOS: not otherwise specified; PE: pulmonary embolism; T2DM: type 2 diabete mellitus.

Table 3. Summary of COVID-19 cases with GI histopathology findings in biopsies and resection specimens.

Case	Reference	Patient Age (y)	Patient Sex	Clinical characteristics	GI pathology findings	Additional investigations	Treatment	Outcome
1	9, 10	**78**	M	- Patient presented with cough and fever for 7 days. - HD 1: fever, stable vital signs, SaO_2 > 95%; positive SARS-CoV2 rRT-PCR testing of nasopharyngeal and oropharyngeal swab specimens; multiple ground-glass opacities in both lungs on chest CT. - HD 4: severe respiratory distress; decreased PaO_2/FiO_2 (130); extensive bilateral consolidation on chest X-ray. - HD 10: upper GI bleeding; mainly esophageal mucosal lesions on endoscopy; biopsy samples were taken from esophagus, gastric, duodenum and colon.	No significant damage: occasional lymphoplasmacytic inflammation and edema in the esophageal mucosa, gastric lamina propria, duodenal and rectal mucosae.	IFL: ACE2+ NP+ in gastric, duodenal, and rectal epithelial cell; weak expressions in the esophageal mucosa.	Empiric anti-microbials, oseltamivir, moxifloxacin, intubation, MV, V-V-ECMO.	- Stable vital signs with mechanical ventilation, V-V-ECMO and low dose vasopressors on HD 26. - No obvious evidence of other organs dysfunction.

Continued

2	16	**NA**	**NA**	- Patient admitted for rectal adenocarcinoma, underwent surgical resection. - POD3: fever and cough. - POD7: throat swab samples tested positive for SARS-CoV2 by qRT-PCR; bilateral ground-glass opacities of subpleural lung parenchyma. - POD14: ground-glass opacities, consolidation, irregular linear fibrosis, irregular fibrosis foci.	No significant mucosal damage: abundant lymphocytes and macrophages infiltrating the lamina propria.	Electron microscopy: SARS-CoV-2 virions in the rectal tissue qRT-PCR detected SARS-CoV-2 nucleic acid in the rectal specimens IHC: NP+ on intestinal epithelial cells, lymphocytes and macrophages in the lamina propria.	NA	- POD41: Patient was discharged after 2 consecutive negative qRT-PCR test results and absence of clinical symptoms and radiological abnormalities. - POD72: throat and rectal swab samples tested negative for SARS-CoV-2 nucleic acid.
3	11	**69**	**M**	- Patient with hypertension admitted with respiratory failure. - Reduced left ventricular ejection fraction on echocardiography. - Circulatory collapse ensued with mesenteric ischaemia and small intestine resection was performed.	Prominent endothelitis of small intestine submucosal vessels and apoptotic bodies.	IHC: ACE2+ on endothelial cells	NA	Patient survived.
4	13	**67**	**M**	- Obese patient, T2DM, hypertension, hyperlipidemia, left bundle branch block. - Fever and chill for 8 days, cough and shortness of breath for 3 days. - Nasal swab positive testing for SARS-CoV-2 and methicillin-susceptible staphylococcus aureus. - Respiratory failure followed by multi-organ failure. - HD 33: lower GI bleeding, scattered erosions and ulceration on colonoscopy.	Nonspecific acute inflammation, ischemic pattern of injury.	IHC: negative staining for CMV	Multiple medication, anticoagulants, antibiotics, antifungal agents, transfusion, intubation.	- HD 49: GI bleeding resolved spontaneously, patient was discharged.

Continued

5	13	**68**	**M**	- Obese patient, tobacco addiction, T2DM, hypertension, hyperlipidemia, CHD. - Cough, fever, diarrhea and altered mental status for 5 days. - Nasal swab positive testing for SARS-CoV-2 by PCR. - Respiratory failure followed by multi-organ injury. - HD 40: lower GI bleeding, normal bowel caliber with no evidence of obstruction on CT abdomen pelvis, colonoscopic appearance clinically consistent with ischemic colitis.	Focal edema, mildly active nonspecific inflammation.	NA	Multiple medication, anticoagulants, antibiotics, antifungal agents, transfusion, intubation.	- HD 54: GI bleeding resolved spontaneously, patient was admitted to the rehabilitation unit.
6	Present case	**62**	**M**	- Patient presented with nausea and epigastric pain with back irradiation for 2 weeks. - Absence of comorbidity or clear exposure history with COVID-19. - Stable clinical course on presentation. - HD 2: subfebrile fever, vomiting, diarrhea, persistent and severe epigastric pain, elevated serum lipase, no evidence of acute pancreatitis on CT imaging, normal electrocardiogram. - Upper GI endoscopy: rugged appearance of the duodenum. - Nasal swab positive testing for SARS-CoV-2 by GeneXpert.	- Preserve villus height, epithelial dystrophy and denudation. - Marked inflammation in the lamina propria that focally causes glandular damage. - Cytopathic viral effects in residual glands: enlarged cells, vacuolated or ballonised cytoplasm, large smudged nuclei, intranuclear inclusions. - Numerous microthrombi, *ACE2 + on various enterocytes.*	None	Azithromycin, anticoagulant, analgesic, antidiarrheal.	- HD 17: overall clinical condition improved. - HD 22: discharge.

ACE2: angiotensin-converting enzyme 2; CMV: cytomegalovirus; HD: hospital day; IFL: immunofluorescence; IHC: immunohistochemistry; MV: mechanical ventilation; NA: not available; NP: nucleocapside protein; POD: postoperative day; qRT-PCR: quantitative real time reverse transcriptase polymerase chain reaction; rRT-PCR: real time reverse transcriptase polymerase chain reaction; T2DM: type 2 diabete mellitus; V-V-ECMO: veno-venous extracorporeal membrane oxygenation.

patients with digestive symptoms, suggesting that COVID-19 was not initially recognized in these patients, leading to delayed diagnosis, which could negatively affect our patient outcomes [4]. Furthermore, it is known that disease severity increases with age and comorbidities [17]. Fortunately, despite his age and delay in accessing care, our patient had favorable outcomes and was discharged at day 22.

At the time of this report, there is no specific recommended treatment for COVID-19 [18] [19]. In our case, persistent epigastric pain and diarrhea dominated the clinical course. Thus, treatment was essentially supportive with analgesic, antidiarrheal, antibiotic and anticoagulation.

4. Conclusion

The emergence of coronavirus disease 2019 (COVID-19) constitutes a serious threat to global public health. Although endoscopy and histological analysis are not practical for diagnosis, they allow elucidation of the pathophysiology of the disease. Pathologic changes could be attributed to direct virus attack or secondary to immune response or drug-induced. Those changes may be specific in the GI tract and related clinical manifestations should not be overlooked.

Informed Consent

Patient's informed consent has been obtained.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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