




Original Article

Comparison of histopathological findings of patients presenting with acute appendicitis in COVID-19 infected and non-COVID-19 infected patients.

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Abstract

Background: COVID-19 disease has been associated with multiple organs and causes various symptoms depending on the organ involved. Histological findings in the lungs, such as microthrombi, perivascular lymphocytic infiltrate, and necrosis/infarction, can also be seen in the histopathology of the appendix of COVID-19 positive patients.

Methodology: This cross-sectional study was conducted in Dr. Ziauddin Hospital, a tertiary care center in Karachi, Pakistan. In this research article, the histopathology reports of the appendix of COVID-19 positive patients presenting with acute appendicitis, either antigen or PCR positive, are compared with those of non-COVID patients who presented with acute appendicitis. The data was analyzed using SPSS 20.0, and Pearson's Chi-Square and Cramer's V tests were performed for analysis.

Results: Comparing the histopathology reports of COVID-19 positive and non-COVID patients presenting with acute appendicitis, an appendix of COVID-19 positive patients shows microthrombi; perivascular lymphocytic infiltrates, and necrosis/infarction.

Conclusion: Patients who are COVID-19 positive presenting with acute appendicitis should be treated surgically as soon as possible to reduce the risk of acute presentation, ultimately leading to perforation, and not wait for the patient to recover from COVID infection first.

Keywords

COVID-19, Acute Appendicitis, Histopathological Findings.



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Introduction

Coronavirus disease-19 (COVID-19), a WHO declared a global pandemic, is caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2)¹. Fever, dry cough, myalgia, tiredness, dyspnea, and anorexia were common symptoms during the onset of the disease. However, many individuals also reported gastrointestinal symptoms and anosmia/dysgeusia². Abdominal pain and pathological features resulting in abdominal discomfort in adult COVID-19 infections are reported in the 2.2–5.8% region in cohort studies^{2,3}. Few cases of COVID-19 presenting with acute abdomen features of pancreatitis and appendicitis have also been reported^{4,5}. Many studies revealed that fewer or the same number of patients presented with acute appendicitis to the emergency room during the COVID-19 pandemic compared to the non-pandemic period, and those who did, presented with complication⁶⁻⁸. We need to consider COVID-19 as a possible diagnosis, even in the event of an abdominal pain syndrome suggesting acute appendicitis. Before emergency surgery, screening for a co-infection can modify the treatment and reassess the therapeutic proposal⁹.

The etiology of appendicitis may be caused by various infections like viruses, bacteria, and parasites regarding the COVID-19 virus; this has been unknown. COVID-19 virus has not been associated with appendicitis. Still, this virus affects multiple organs, causing various symptoms, with respiratory failure being the most common symptom associated with COVID-19. Researchers have shown that the COVID-19 virus can also be isolated from rectal swabs and feces and can show various non-respiratory symptoms (e.g., diarrhea, headache, nausea). It is unnecessary for the COVID-19 virus to show respiratory symptoms¹⁰. Some gastrointestinal symptoms with acute abdomen have been associated with COVID-19 patients and mimic acute appendicitis.

Our research wanted to check if the COVID-19 virus can affect the appendix and affect the intestinal wall due to an increased expression of the viral receptor ACE-II¹⁰.

Our research highlights histopathology findings in acute suppurative appendicitis due to luminal obstruction in non-COVID patients and vascular occlusion such as venous thrombosis commonly seen in COVID-19 positive patients¹¹.

Methodology

This cross-sectional study was conducted in Dr. Ziauddin Hospital North Nazimabad, Karachi, Pakistan. The duration of this study is from March 2020 to February 2021 (the era of the COVID pandemic). Twenty-four patients were selected, 12 of them being COVID positive (antigen or PCR positive) and 12 patients who were confirmed COVID negative both on antigen or PCR.

Data was collected using Ziauddin Hospital's own EMR (Electronic Medical Record). Complete data of the patient from the day of admission to the discharge day, including the history notes, blood investigations, and imaging and their treatments were present.

This patients' sample included those who presented within 7 days history of RIF pain. Patients who presented with right iliac fossa (RIF) pain were diagnosed radiologically and underwent appendectomy, either open or laparoscopic. Their histopathology findings were compared. Findings of the appendix of COVID-19 positive patients were correlated with findings usually found in the lungs of COVID-19 positive patients. Patients who presented after 7 days of RIF pain, those with previous appendectomy or known cases of perforation, and those with known cases of hematological disturbances were excluded.

The data was entered and analyzed using IBM Statistical Packages for the Social Sciences version 20.0. The Pearson's Chi-Square test was performed to compare the COVID positive and COVID negative samples and features of perforation, and a p-value of ≤ 0.05 was considered statistically significant. The Cramer's V test was also performed to check the strength of associations between variables.

Results

There were 24 patients, of which 19 were males and 5 were females. The patient's mean age was 30.4 years and there were 79.16% male and 20.83% female. 24 patients were included in the study, 12 being COVID-19 negative and 12 COVID-19 positive either PCR or antigen. Patients were selected randomly based on gender and age. 5 out of 24 were female, of which 3 were COVID-19 negative and 2 were COVID positive. Age ranges from 16-to

65 years were included. No significance in terms of gender and age. Patients were tested for COVID-19 before admission, and for definitive diagnosis of acute appendicitis, diagnostic imaging was used, i.e., U/S whole abdomen +/- pelvis, CT-FACT, and CT-scan abdomen with contrast. Standard treatment of acute appendicitis was given before surgery. The appendix was removed surgically via laparoscopic approach in 22 patients and open approach in 2 patients. Patients were advised to follow up with a histopathology report in OPD.

Table 1: Compare the COVID positive and negative association with perforation features.

Variables	n	COVID-19		p-value	
		Positive (n=12)	Negative (n=12)		
Gender	Male	19	10(83.33)	0.980	
	Female	05	2(16.66)		
Perforation			10(83.33)	1(8.33)	0.001*

Cramer's V was used to assess the strength of significance and a 0.7 (V=0.7) value, showing a strong relationship between the two variables. Results are presented as n(%), and Row-wise percentages were computed. *Significant (p<0.05).

The histopathological findings of COVID PCR/antigen-positive patients with acute appendicitis were (Table 1). All patients n=12 (100%) showed extensive surface ulceration and inflamed granulation tissue. Ten of the twelve patients (83.3%) showed dense transmural deposits of lymphocytes and plasma cells in muscularis propria extending to surrounding fat along with neutrophils. One patient (8.3%) of the remaining two showed only neutrophils, whereas the other (8.3%) showed mixed infiltrates. Ten of the twelve patients (83.3%) showed focal areas of necrosis, while in the remaining two patients (16.7%), areas of necrosis were not seen. Ten of twelve patients (83.3%) showed features of transmural infarction secondary to microthrombi suggestive of perforation, but in two patients (16.7%), there were no signs of thrombi. There is no evidence of granuloma or malignancy in all patients n=12 (100%).

While the findings in the histopathology of non-COVID patients showed Extensive surface ulceration and inflamed granulation tissue in n=12 (100%) and dense infiltrate of neutrophils with few lymphoplasm cells in n=9 (75%) patients. Only

n=3 (25%) patients had a predominance of lymphocytes. Only one patient (8.3%) showed local areas of necrosis with abundant neutrophils and no thrombi in n=12 (100%) patients. One patient (8.3%) had evidence of malignancy (Low-grade Appendiceal Mucinous Neoplasm).

The findings suggest an association between COVID infection and perforation in acute appendicitis. Features of perforation were seen in n=10 (83.3%) of COVID positive patients compared to only n=1 (8.3%) of non-COVID patients (p=0.001) on the chi-squared test suggesting a significant association. Cramer's V was further used to assess the strength of this significance, and a value of 0.7 was obtained, showing a strong relationship between the two variables. The result shows a highly atypical histological appearance of appendix specimens of COVID positive patients, such as occasional microthrombi, transmural necrosis or infarction, and perivascular lymphocytic infiltrate compared with non-COVID patients whose histological appearance does not show these findings. These findings in COVID-19 positive appendix may lead to acute presentation and early perforation, which increases mortality.

Table 2: COVID-19 PCR/ ICT positive and negative patients.

Variables	N(%)	
	Positive patients	Negative patients
Surface ulceration + inflamed granulation tissue	12(100)	12(100)
Perivascular infiltrates (predominantly)	Lymphocytes	10(83.3)
	Mixed	1(8.3)
	Neutrophils	1(8.3)
Necrosis/ Infarction	Present	10(83.3)
	Absent	2(16.6)
Thrombosis	Present	10(83.3)
	Absent	2(16.6)
Evidence of granuloma or malignancy	Yes	-
	No	12(100)
Impression	Acute suppurative Appendicitis with Periappendicitis & features of perforation	2(16.6)
	Acute Appendicitis with Periappendicitis & features of perforation	6(50)
	Gangrenous Appendicitis with features of perforation	2(16.6)
	Acute Early Appendicitis	2(16.6)
	Fibrous obliteration of tip of the appendix	-
	Benign Follicular Lymphoid Hyperplasia of Appendix	-
	Low-grade Appendiceal Mucinous Neoplasm	-



Figure 1: The circle shows the viable portion of the appendix while the arrows show the necrotic portion of the appendix - 10x.

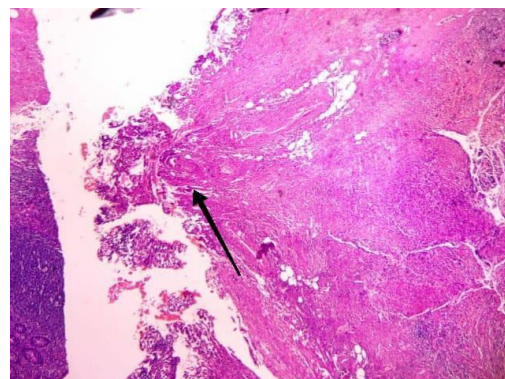


Figure 2: Amorphous granular debris within a distinct inflammatory border - 10x.

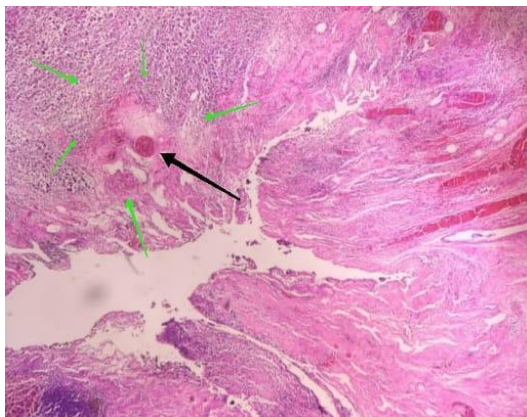


Figure 3: Black arrow showing microthrombi lodge in a vessel and green arrows showing perivascular infiltrates and necrotic slough - 10x.

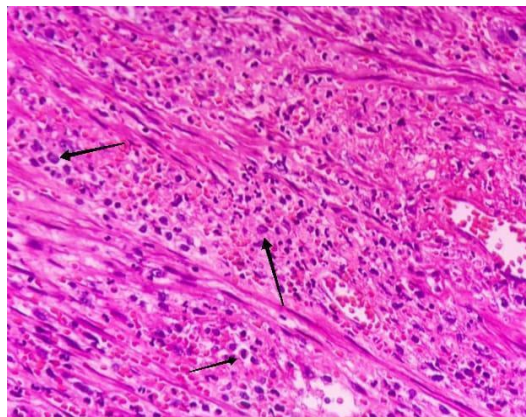


Figure 4: Perivascular infiltrates lymphocytes predominantly with a moderate amount of neutrophils - 40x.

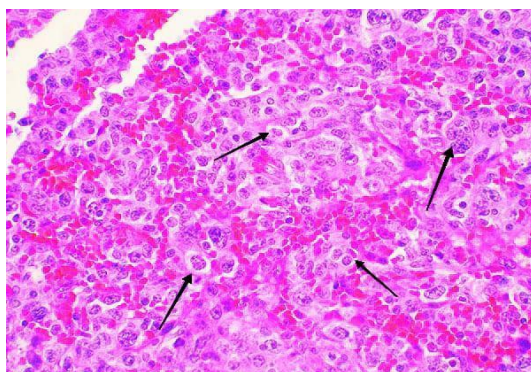


Figure 5: Numerous amounts of lymphocytes in the muscularis propria of the appendix - 40x.

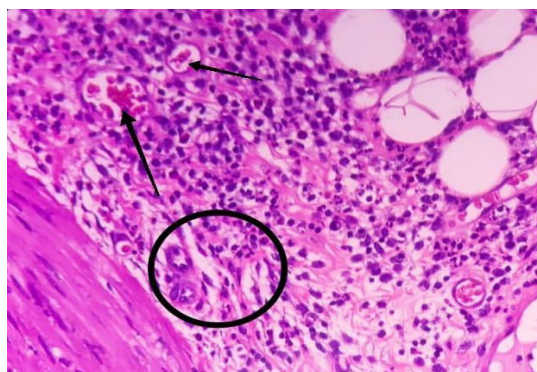


Figure 6: Arrows showing vessels lodged with microthrombi, and the circle shows necrotic areas- 40x.

Discussion

The first case of the coronavirus was seen in Wuhan, China, which gradually spread across the entire world, becoming a pandemic. Coronavirus disease (COVID-19) is believed to be transmitted through respiratory droplets, but other modes of transmission are not completely ruled out and need further researches¹².

Conservative management with antibiotics for uncomplicated appendicitis has the risk of recurrent appendicitis, and ranges from 16% to 40% at one year after initial treatment^{13,14}. Patients who are COVID-19 positive presented have mainly respiratory symptoms. Still, non-respiratory symptoms such as diarrhea, headache, and nausea

can also co-exist, and most of the time, these symptoms are the only presenting complains¹⁴. GI symptoms occur in 11-64% of COVID-19 positive patients. So huge concern is there about GI problems in COVID-19 patients because almost half of the patients do not show respiratory symptoms¹⁵. In other research, 733 patients were included in the 2019 cohort, and 422 patients were included in the 2020 cohort. In 2019, 32.7% had positive CT findings, increasing to 50.5% in 2020. The number of complications increased from 7.9% to 19.7%. The rate requiring surgical intervention increased from 26.3% to 47.6% in 2020¹⁶. The SARS-CoV-2 virus has been shown to replicate through enterocytes and can only be detected by biopsy¹⁷. Another hypothesis is that it can act

through increased expression of viral receptor ACE-II¹⁸.

In the UK, during this pandemic, Soeselo et al. presented the first case report of SARS-CoV-2 infection that directly infected the appendix, causing acute appendicitis, in which highly atypical histopathological features such as microthrombi, perivascular lymphocytic infiltrates and infarction were found and later confirmed by a polymerase chain reaction of appendicular tissue sample which was positive¹⁹. Intraluminal pathologies probably play a major role in the development of acute appendicitis. Intraluminal pathological findings may also be seen in healthy persons without necessarily pointing to acute appendicitis²⁰. In our study, the histopathological reports of appendix specimens were compared between the COVID-19 positive and non-COVID patients. Extensive surface ulceration along with inflamed granulation tissue is found in every patient showing typical acute appendicitis. In non-COVID patients, perivascular neutrophilic infiltrates were present, while in COVID-19 positive patients, predominantly lymphocytes were present. Ten of the twelve patients who were COVID-19 positive patients showed focal patches of necrosis on the wall and transmural infarction secondary to microthrombi. These patients showed features of perforation. Patients with CT-proven, uncomplicated appendicitis, antibiotic treatment did not meet the prespecified criterion for noninferiority compared with appendectomy. Most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-year follow-up period, and those who required appendectomy did not experience significant complications²¹. The management of acute appendicitis in the UK, with non-operative management shown to be safe and effective in the short-term. Antibiotics should be considered as the first line during the pandemic and perhaps beyond²².

In non-COVID, only one patient had local areas of necrosis without abundant lymphocytes and microthrombi. There was no evidence of granuloma or malignancy in COVID-19 positive

patients, while in non-COVID, histopathology of one patient showed evidence of Low-grade Appendiceal Mucinous Neoplasm. These are the findings typically seen in the specimen of lungs of COVID-19 patients. This comparison concludes that COVID-19 patients should be treated as early as possible to decrease the risk of acute presentation leading to necrosis or infarction, which may ultimately lead to perforation. In comparison with non-COVID, patients presenting early with acute appendicitis are without complications. This may be due to the patient's concerns about exposure to COVID-19 in hospitals, leading to a delay in presentation. This delay is related to complications. The fear of contracting COVID-19 in hospitals prevents the patients from seeking timely care, which can be correctable or curable if present early²³.

COVID-19 virus has been known to cause thromboembolic complications in multiple organs, such as pulmonary embolism, hemorrhagic colitis, and systemic condition like disseminated intravascular coagulation. A higher incidence of coagulopathy caused by the COVID-19 virus in various organs leads to further complications²³. Still, some studies show that during this pandemic, patients with symptoms of acute appendicitis that presented late were with more severe condition²⁴. A case report showed bowel necrosis in a patient with COVID-19 positive that is present in the ER as peritonitis. Thus higher suspicion is needed when dealing with patients with surgical problems who are diagnosed with COVID-19. The same features should be in mind to managing such surgical conditions when treating patients with coronavirus.

As our research shows focal areas of necrosis and transmural infarction in COVID-19 positive patients, the rate of perforation is then increased in these kinds of patients. As mentioned earlier, these findings may be secondary to vascular occlusions, such as venous thrombosis. These vascular occlusions are due to neutrophil extracellular traps (NET) found in the blood vessels in organs. According to some research, these NETs are the cause of vascular occlusion²⁰. This is compared to the non-COVID patients whose most common

etiology is luminal obstruction either by fecalith or lymphoid hyperplasia⁵.

In this COVID-19 pandemic, patients with uncomplicated appendicitis can be treated via IV antibiotics without being complicated, although the gold standard is appendectomy either in uncomplicated or complicated cases. Most surgeons advise IV antibiotics in uncomplicated acute appendicitis to avoid direct exposure during surgery^{6,7}. This is applicable in non-COVID patients presenting with appendicitis. Still, in the case of COVID-19 positive patients, this region is where more research is required to justify the role of conservative management. As the IV antibiotics are distributed in the body through blood vessels, in the COVID-19 positive patients, the vascular occlusion inhibits the antibiotics molecule from reaching the destination point and results in no improvement. Instead of improving, the condition can become critical due to delays in definitive management. This hypothesis can cause devastation for medical healthcare professionals.

A case was reported in the USA in which a patient with COVID-19 positive was diagnosed with acute appendicitis and then treated conservatively with IV antibiotics for 7 days, which improved the symptoms of the patient. Although there is not much evidence to prove the benefits of IV antibiotics in managing COVID-19 positive appendicitis, further research should be carried out on this high yield topic⁸. Furthermore, emergency cases like appendicitis should be operated on without any delay in COVID-19 suspected patients to avoid complications related to COVID-19 virus⁹.

Based on histopathological reports of appendix specimens of COVID-19 positive and non-COVID appendicitis patients, we compared the histological findings, which are atypical in COVID-19 positive patients, such as occasional microthrombi, perivascular lymphocytic infiltrate, and necrosis/infarction. There are perforation features in COVID-19 positive appendix which shows the urgent requirement of appendectomy; if not can result in perforation leading to increased mortality. The role

of antibiotics in appendicitis of COVID-19 positive patients is still controversial.

The limitations of the study include small sample size because only twelve COVID-19 positive patients were operated as appendectomy during this pandemic in the center. Moreover, it was a single-center study which was another major limitation.

Conclusion

It is concluded that the patients who were infected with COVID-19 positive, despite having mild symptoms, should be treated as soon as possible because of hematological disturbances created by the COVID-19 virus, which can lead to acute presentation with an increased risk of necrosis or infarction of the appendix ultimately leading to perforation. Furthermore, these patients cannot be treated conservatively with antibiotics because of the vascular occlusion caused by microthrombi. This article highlights the comparison of histopathological findings of appendix in COVID and non-COVID patients, which showed microthrombi, perivascular lymphocytic infiltrate, and necrosis/infarction in COVID positive patients. This may lead to the early perforation of the appendix as compared to the appendix of non-COVID patients and then peritonitis. Therefore we suggest such patients should be treated immediately only by the surgical method to decrease the risk of acute presentation, which may lead to an increased risk of perforation.

Conflicts of Interest

The authors have declared that no competing interests exist.

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