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Cholecystitis as a Possible Immunologic Consequence of COVID-19; Case Series from a Large Healthcare System

Dear Editor:

Gastrointestinal manifestations are seen in COVID-19 disease, but biliary disease has been less well described.[1] A few cases of cholecystitis have been described related to COVID-19 disease.[2-5] The described cases of cholecystitis in individuals with SARS-CoV-2 were postulated to be mediated by a dysregulated immune response to SARS-CoV-2 infection.[2-5] Two cases reporting cholecystitis related to COVID-19 were at onset of COVID-19 symptoms,[2] but most cases described cholecystitis lagging COVID-19 diagnosis by at least 10-14 days or longer.[3-5] This timing later in the COVID-19 disease course supports an immune mediated mechanism triggering biliary pathology.[6] We examined clinical characteristics of cholecystitis presenting in SARS-CoV-2 infection at our institution.

This is a retrospective case series of patients with a diagnosis of COVID-19 and cholecystitis in the Atrium Health system. We identified all encounters with International Classification of Diseases, Tenth Revision (ICD-10) codes for COVID-19 (U07.1), and cholecystitis (K81.0, K81.9) between March 1, 2020, and March 1, 2021. All patients included had a confirmed positive test for SARS-CoV-2 by either Roche Cobas® (Roche Diagnostics, Indianapolis, IN) or Luminex ARIES® or NXTAG® (Luminex Corp, Austin, TX) nasopharyngeal PCR for SARS-CoV-2 between March 1, 2020, and December 1, 2020. We identified individuals who were diagnosed with cholecystitis within 1 week prior or 3 months following an initial positive SARS-CoV-2 test. Date of confirmatory imaging (either computerized tomography (CT), ultrasound, or cholescintigraphy), was used as the diagnosis date for cholecystitis. All qualified patients had retrospective review of their health system electronic medical record (EMR).

Thirty patients were diagnosed with cholecystitis within 3 months of COVID-19 infection - half female (n=16) and obese (n=17 with a body mass index greater than or equal to 30 kg/m^2), most (n=27) had symptom onset at home, and only 10 had respiratory symptoms with none being critically ill at time of cholecystitis presentation. Fourteen patients were diagnosed with SARS-CoV-2 infection at time of their presentation with cholecystitis, usually due to pre-operative assessment; 6 patients never manifested symptoms aside from cholecystitis. Of 16 patients who were diagnosed with COVID-19 prior to presentation of cholecystitis, 13 had respiratory symptoms with mean time between COVID-19 and cholecystitis symptom onset of 24 days (5 – 84 days). For all 16 patients, a mean of 17 days (4-85 days) elapsed between testing positive for SARS-CoV-2 and cholecystitis diagnosis (see Fig. 1). Fewer patients who were diagnosed with SARS-CoV-2 infection at cholecystitis presentation had respiratory symptoms compared to those with earlier manifestations of COVID-19, but the two cohorts were otherwise similar.

While 17 patients required hospitalization for COVID-19, most had mild disease with 8 hospitalized only for cholecystitis and only 9 requiring oxygen, 3 requiring mechanical ventilation, 5 treated with Remdesivir and 6 with steroids. Seventeen patients underwent cholecystectomy. Interestingly, surgery did not appear to impact outcome: symptoms resolved in 8 of 10 (80%) individuals who underwent surgery and 15 of 18 (83%) who did not undergo surgery and were alive at 30 days. 6 patients had delayed surgery over 30 days following diagnosis, but none had residual symptoms at 30 days prior to surgery. Excluding 2 patients who died, one of 4 patients (25%) who received steroids required surgery, while 16 of the remaining 24 patients (67%) required surgery. The two deaths were due to respiratory failure from COVID and unrelated to cholecystitis (Table 1).

Cholecystitis may be an uncommon complication of COVID-19. During the same time period of our 30 reported cases of cholecystitis, 35,814 patients tested positive for SARS-CoV-2 in our healthcare system. As several patients had no COVID-19 related symptoms aside from those for cholecystitis, it is possible that some of our cases represent coincidental development of cholecystitis. However, individuals undergoing cholecystectomy at our institution were more likely to have SARS-CoV-2 infection than the overall population undergoing routine pre-operative testing with 15 of our patients with SARS-CoV-2 infection undergoing surgery between April 15, 2020, and December 1,2020, during which time 186 patients underwent routine pre-operative testing for SARS-CoV-2 infection prior to cholecystectomy. This 8% incidence rate of SARS-CoV-2 infection prior to cholecystectomy compares to a 1.3% incidence of SARS-CoV-2 infection (n=1024) on all routine pre-operative testing (n=81130) during the same period.

This increased incidence of disease and the timing of disease with distribution of cholecystitis symptom onset clustered around 17 to 24 days following SARS-CoV-2 infection, rather than in a random distribution, suggests a relationship with immune inflammatory related pathology.

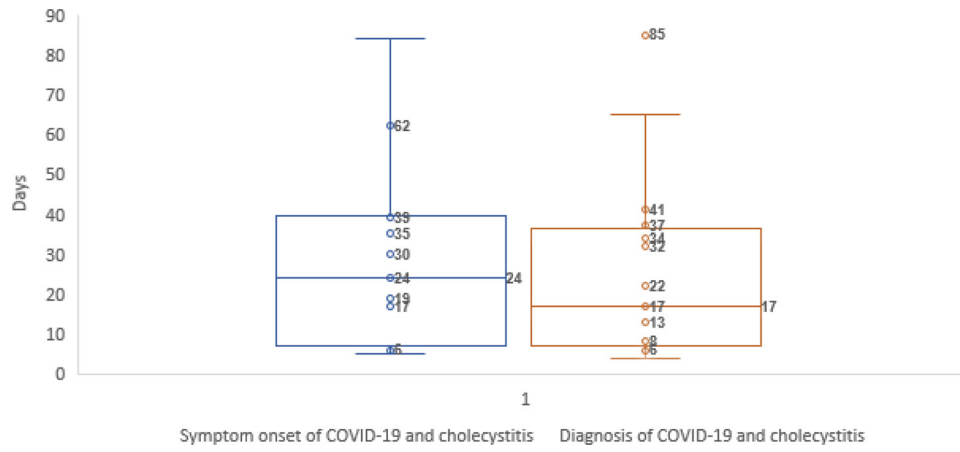

FIGURE 1. Time between COVID-19 and cholecystitis.

This timing is similar to the recently described Multisystem Inflammatory Syndrome in Children (MISC-C) and adults (MIS-A) following SARS-CoV-2 infection.[7-9] The hyperinflammatory immune response following SARS-CoV-2 infection is responsible for MIS-C and MIS-A,[9] and given similarities in timing, we hypothesize that cholecystitis in our patients could be driven by immune activation. None of our patients were diagnosed with MIS-A though. Finally, our observation of decreased need for surgery in patients treated with steroids also supports an inflammatory mechanism of disease. Clinicians should remain attune to the presentation of cholecystitis related to SARS-CoV-2 infection due to immune activation in COVID-19 disease.

TABLE 1. Patient Characteristics

Variable	n=30 (%)
Mean Age [range] years	54 [21-90]
Sex	
Female	16 (53)
Male	14 (46)
Race / Ethnicity	
White	18 (60)
Black	9 (30)
Hispanic	8 (23)
Mean BMI [range] kg/m^2	30 [19 – 49]
Signs and Symptoms	
Abdominal pain	20 (67)
Subjective Fevers	13 (43)
Documented Fever (>100.4)	7 (23)
Nausea/Emesis	15 (50)
Diarrhea	5 (17)
Respiratory symptoms at time of cholecystitis	10 (33)
Location at symptom onset	
Pre-admission	27 (90)
Inpatient	3 (10)
Cholecystitis	
Calculus	22 (73)
Acalculus	9 (27)
Median Labs [range] at diagnosis	
Alanine transaminase (ALT) IU/L	32 [7 – 256]
Aspartate aminotransferase (AST) IU/L	25 [12 – 282]
Alkaline phosphatase (ALP) IU/L	78 [42 – 422]
Total bilirubin mg/dL	0.7 [0.2 – 1.5]
Maximum C-Reactive protein (CRP) mg/ dL	16 [0.5 – 29]
Treatment	
Observation alone	3 (10)
Antibiotics	22 (73)
Percutaneous drain	11 (37)
Surgery	17 (57)
Mean Time from Dx to Surgery	26 days
Resolution of Symptoms at 30 Days	
With surgery	8/11 (73)
Without surgery	15/19 ((79)
30-day Mortality	2 (6)

AUTHOR CONTRIBUTIONS

All authors had full access to and take responsibility for the data reports. C.P., M.S., and M.L were responsible for the conception and design of the study, T.L. performed data extraction, and all authors contributed to data collection, writing, and revising the manuscript.

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