Case Report

Coronavirus disease 2019 and extra-pulmonary tuberculosis co-infection – A case report and review of literature

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ABSTRACT

The Coronavirus disease 2019 (COVID-19) pandemic continues to cause significant global morbidity and mortality, leading to the need to study the course of the disease in different clinical circumstances and patient populations. While co-infection between COVID-19 and many pathogens has been reported, there has been limited published research regarding co-infection with Mycobacterium tuberculosis. We describe a case of co-infection involving COVID-19 and extra-pulmonary tuberculosis in a patient with cirrhosis, and review the current literature regarding COVID-19 and tuberculosis co-infection. In spite of several co-morbidities that have been shown to portend a poor prognosis in patients with COVID-19 infection, our patient fully recovered.

1. Introduction

Coronavirus Disease 2019 (COVID-19), occurring due to the novel severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2), was first reported in Wuhan, China in December 2019 [1]. Since then, more than 48 million cases with more than 1,231,000 deaths have been reported globally [2].

Since its worldwide spread, co-infection between COVID-19 and numerous pathogens has been reported [3,4]. However, the incidence and outcomes of mycobacterial co-infection is less well-described. Amongst the different co-morbidities associated with worse outcomes in COVID-19 patients, hepatic cirrhosis has been associated with worsening liver function and 30-day mortality rates as high as 34% [5].

We report a patient with cirrhosis with symptomatic COVID-19 infection, who was also diagnosed with extra-pulmonary Mycobacterium tuberculosis (TB) infection during the same hospital admission. We also review the existing literature on potential co-infections between these two pathogens.

2. Case

A forty-nine year old man from El Salvador, with a history of daily alcohol use for twenty years, presented to our hospital in April 2020 with a two-week history of burning, diffuse abdominal pain radiating to his back, worsening abdominal distension, non-productive cough and orthopnea.

In the emergency room, he was febrile (100.3 °F) and mildly hypoxic [oxygen saturation (SPO2) 93% on 2–3 L/min oxygen by nasal cannula]. Physical examination revealed decreased bibasilar air entry, abdominal distension with shifting dullness and no signs of chronic liver disease. Significant admission laboratory testing included hyponatremia (Table 1) and elevations in liver enzymes (Table 1), international normalized ratio (Table 2) and inflammatory markers (Table 3).

Computed tomography (CT) scan of the abdomen and pelvis revealed large-volume ascites with peritoneal hyperattenuation, heterogeneous nodular liver, bibasilar pleural effusions, and tree-in-bud pulmonary opacities [Fig. 1]. Paracentesis yielded serosanguinous fluid with unremarkable cytology (Table 4). The serum ascites albumin gradient was 1.3 g/dl (consistent with portal hypertension), but the elevated ascitic fluid protein suggested an exudative process. COVID-19 was diagnosed by reverse-transcriptase polymerase chain reaction testing on a nasopharyngeal specimen.

Based on the hospital’s COVID-19 treatment protocol, he was started on oral hydroxychloroquine (800 mg, followed by 400 mg daily for 4 days), which was discontinued after 3 doses due to concern for hepatoxicity in the setting of cirrhosis. He received one infusion of

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Table 1
Admission Complete Metabolic Panel.

| Laboratory parameter | Results | Normal Range |
|----------------------|---------|--------------|
| Sodium (mmol/L)      | 130     | 135-145      |
| Potassium (mmol/L)   | 3.5     | 3.5-5.3      |
| Chloride (mmol/L)    | 92      | 98-107       |
| Carbon Dioxide (mmol/L) | 24    | 22-31        |
| Anion gap (mmol/L)   | 14      | 7-14         |
| Blood urea nitrogen (mg/dL) | 8    | 7-23         |
| Creatinine (mg/dL)   | 0.66    | 0.5-1.3      |
| Glucose (mg/dL)      | 91      | 70-99        |
| Calcium, Total (mg/dL) | 8.1    | 8.4-10.5     |
| Protein (g/dL)       | 7.1     | 6.0-8.3      |
| Albumin (g/dL)       | 2.6     | 3.3-5.0      |
| Bilirubin, Total (mg/dL) | 1.6    | 0.2-1.2      |
| Alkaline Phosphatase (U/L) | 250 | 40-120       |
| Aspartate Aminotransferase (U/L) | 110 | 40-120       |
| Alanine Aminotransferase (U/L) | 49    | 4-41         |
| eGFR if non-African American (ml/min/1.73 M²) | 114 | ≥ 60         |

Table 2
Admission hematologic and coagulation parameters.

| Laboratory parameter | Results | Normal Range |
|----------------------|---------|--------------|
| White Blood Cell Count (K/µL) | 4.91 | 3.8-10.5 |
| Hemoglobin (g/dL)      | 15.7    | 13.0-17.0    |
| Hematocrit (%)         | 46.9    | 39.0-50.0    |
| Platelets (K/µL)       | 234     | 150-400      |
| Prothrombin time (seconds) | 14.3 | 10.6-13.6   |
| Activated partial thromboplastin time (seconds) | 37.2 | 27.5-35.5 |
| Protime/International Normalized Ratio (INR) (ratio) | 1.24 | 0.88-1.16 |

Table 3
Markers of inflammation.

| Laboratory parameter | Results | Normal Range |
|----------------------|---------|--------------|
| D-dimer (ng/ml DDU)  | 2979    | <229         |
| Ferritin (ng/ml)     | 549     | 30-400       |
| C-Reactive Protein (mg/dL) | 2.48 | 0-0.40       |
| Lactate Dehydrogenase (U/L) | 290 | 50-242       |
| Procalcitonin (ng/ml) | 0.23 | <0.2         |

convalescent plasma on hospital day 4 as part of a clinical trial, but did not meet criteria for remdesivir infusions. His oxygen requirement completely resolved by day 7. Work-up for bacterial and fungal co-infections, including four sets of blood cultures, remained negative.

Given his CT findings and endemic risk factors for TB, repeat paracentesis with testing for acid-fast bacilli (AFB) and adenosine deaminase (ADA) levels was performed. Additionally, serum QuantiFeron and sputum AFB testing were sent. His hospital course was complicated by ascitic fluid re-accumulations requiring large volume paracenteses and worsening hyponatremia with acute kidney injury (peak serum creatinine 2.1 mg/dL), managed with albumin infusions and fluid restriction. Although he displayed clinical improvement, he continued to have intermittent fevers that were presumed to be secondary to COVID-19. AFB sputum testing, QuantiFeron and peritoneal fluid ADA testing were all unremarkable, however peritoneal fluid cultures grew Mycobacterium tuberculosis (TB). CT scan of the chest to evaluate for concurrent pulmonary TB revealed a large left and small loculated right pleural effusion, calcified hilar lymph nodes, and patchy right lung opacities [Fig. 2]. Thoracentesis demonstrated hazy fluid with 117 lymphocyte-predominant nucleated cells/µL, negative bacterial and AFB stains and cultures, and an unremarkable ADA level. The etiology of the effusions remained unclear – differential diagnosis included hepatic hydrothorax or atypical presentation of COVID-19; it resolved with supportive care. Given the lack of alteration in treatment and isolation already in place due to COVID-19 and risks of aerosolization, no further AFB sputum sampling was pursued.

On hospital day 21, he was started on a four-drug anti-tuberculous regimen: rifampin, isoniazid, ethambutol, and levofloxacin. Pyrazinamide was replaced by levofloxacin to decrease the hepatotoxicity risk (given his underlying advanced cirrhosis). He was discharged after a six-week hospital stay and tolerated the four-drug therapy well. After two months, the regimen was narrowed to rifampin and isoniazid. Outpatient upper endoscopy confirmed esophageal varices and portal hypertensive gastropathy. By three months after discharge his ascites was well controlled with diuretics.

3. Discussion

There are few large-scale studies that have reported the association of COVID-19 with TB [6-9]. There have been anecdotal reports on COVID-19-TB coinfection, with outcomes varying from complete recovery [10] to death [11].

An early observational study in China postulated that latent/active TB was a significant risk factor for COVID-19 [6]. TB Patients were reported to have a higher incidence of COVID-19, faster disease progression and more severe disease. However, this study had a small sample size and an unclear diagnostic approach, with TB diagnosis based on interferon-gamma release assay testing alone. There were no details on sputum AFB testing or on differentiation between latent and active infections. An Italian study evaluated the occurrence of COVID-19 in patients with known active pulmonary and/or extra-pulmonary TB in the same hospital unit, with mixed results [7]. 63% of co-infected patients had improvement in their tuberculosis lesions, while 35% had worsening disease [with one subsequent death (20% case-fatality rate)]. The authors attributed a modest overall impact of COVID-19 on the clinical course of TB patients [7]. Another large multinational observational study [8] examined the occurrence of COVID-19 with both pulmonary and extra-pulmonary TB and found a 12.3% case-fatality rate.

It is not clear whether COVID-19 precipitates latent TB reactivation or whether TB infection conversely predisposes to infection by the SARS-CoV-2 virus. SARS-CoV-2 has been thought to produce an exaggerated inflammatory response (“cytokine storm”) [12], that may result in immune activation and exacerbation of latent/occult infections. Additionally, the use of immunosuppressive medications in COVID-19 patients [13] may lead to unmasking of TB – these medications are known to cause reactivation of mycobacterial infections [14]. Our patient did not receive any immunosuppressive therapy for COVID-19.

Another interesting observation is the proposed protection against COVID-19 conferred by the Bacille Calmette-Guérin (BCG) vaccine. This is extrapolated from reports of the vaccine’s activity against respiratory syncytial virus, influenza A virus and herpes simplex virus type 2 [15,16]. Some studies have reported BCG’s potential protective effect against COVID-19 [17-19]; however, this has not been replicated in larger studies [8,9] and has been critically reviewed [20]. There are ongoing trials evaluating the BCG vaccine and recombinant BCG vaccine VPM1002 [trial numbers NCT04347876 and NCT04387409 respectively] for their ability to protect against COVID-19.

Tuberculosis and COVID-19 may also be linked from a public-health standpoint. The quarantine measures for COVID-19 may result in inadvertent discontinuation of anti-tuberculous therapy and loss of patient follow-up [21]. However, the isolation measures may result in a
decrease in TB infections – one study noted a decrease in confirmed TB cases in 2020 (compared to previous years) [22]. Mathematical models have shown that in the absence of adequate primary prevention measures, an earlier and higher peak of COVID-19-TB coinfections (with more severe disease) may occur [23].

Our patient had a confirmed COVID-19 infection, followed by diagnosis of peritoneal TB with no prior history of TB. Interestingly, he had a full recovery despite having cirrhosis, portal hypertension, and this co-infection. Poor outcomes have been reported in COVID-19 patients with cirrhosis and portal hypertension [5], and the combination of TB infection and cirrhosis also demonstrates increased mortality [24,25]. It is unclear whether co-infection with TB and SARS-CoV-2 leads to significant differences in outcomes, or if one infection predisposes to the other. Further research is needed to analyze the pathogenetic inter-relationship between the two infections and to assess long-term outcomes of co-infections.

### Table 4
Admission Ascitic fluid test results.

| Laboratory parameter | Results | Normal Range |
|----------------------|---------|--------------|
| Color                | Serosanguinous | No color |
| Total Nucleated Cell Count (cells/µL) | 670 | < 500 |
| Total Red Blood Cell Count (cells/µL) | 550 | 0 |
| Fluid Segmented Granulocytes (%) | 7 | < 25% |
| BF Lymphocytes (%) | 78 | No established reference |
| Monocyte macrophage count (%) | 12 | No established reference |
| Mesothelial Cells (%) | 3 | No established reference |
| Albumin, Fluid (g/dL) | 1.3 | No established reference |
| Protein, Fluid (g/dL) | 3.1 | No established reference |
| Albumin, Serum (g/dL) | 2.6 | 6.0–8.3 |
| Protein, Serum (g/dL) | 7.1 | 3.3–5.0 |

Fig. 1. Computed Tomography (CT) scan of abdomen/pelvis, showing abdominal ascitic fluid (red arrows) with mild nodularity of surface of liver (green arrows). The letter “P” denotes posterior/dorsal orientation of the patient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
4. Conclusion

COVID-19 may occur with other infections and may also lead to unmasking of latent infections such as TB. Clinicians must evaluate COVID-19 patients for other co-infections, particularly those with atypical clinical features. Further research is needed to evaluate the link between TB and the SARS-CoV-2 virus.

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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Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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